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54. TÍTULO

COMBINACION DE POLIGLUCOSAMINA Y FIBRATO PARA LA PREVENCIÓN Y
TRATAMIENTO DE LA HIPERLIPIDEMIA.

51. CLASIFICACIÓN INTERNACIONAL

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A61P 3/06.

71. SOLICITANTE

DNP CANADA INC.

DOMICILIO

MONTREAL, QUEBEC, CANADA.

74. APODERADO

DILIA RODRIGUEZ D'ALEMAN

22. BOGOTÁ, D. C.,

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

2

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TÍTULO (54)

COMBINACIÓN DE POLIGLUCOSAMINA Y FIBRATO PARA LA PREVENCIÓN Y TRATAMIENTO DE LA HIPERLIPIDEMIA.

7

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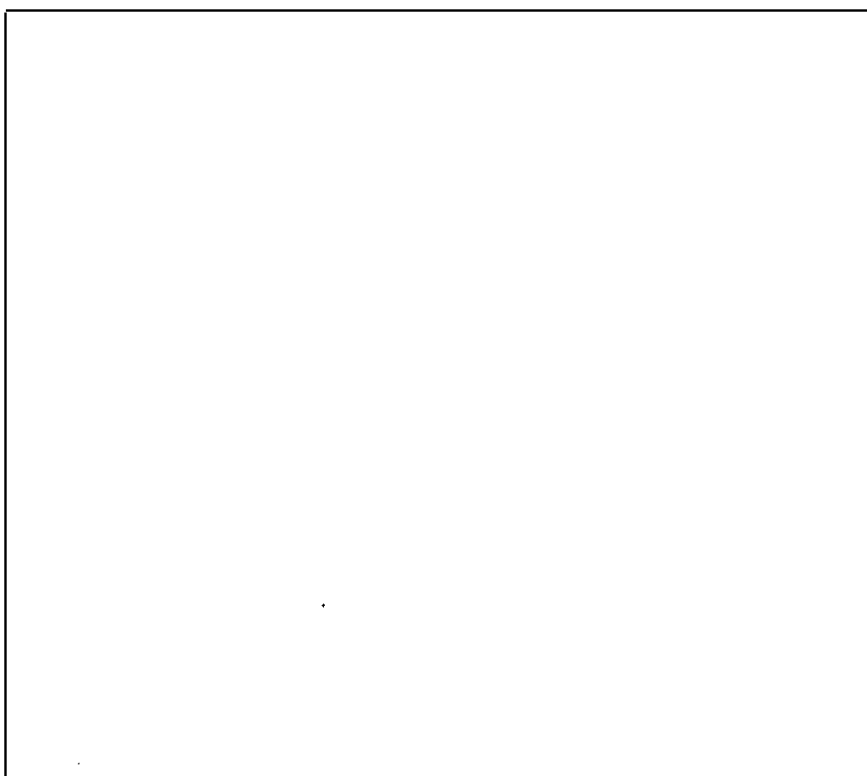
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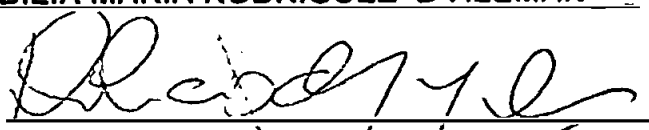
9

Comprobante de pago No. 08-22.407 // 08-24.789 Fecha 13/03/08 // 27/03/08

- ☐ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☐ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso copia de contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de deposito del material biológico
- ☐ Arte final 12 X 12 .
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
- ☐ Otros * Opinión escrita. * Request, * IB301, IB308, RO105, RO135.

11 FIGURA CARACTERÍSTICA**12 Solicito la concesión de la patente**NOMBRE : DILIA MARÍA RODRÍGUEZ D'ALEMAN

FIRMA:


C.C. 41.654.882 / T.P. 20824

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 22,407
FECHA : MARZO 13 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Mr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	062754387	2661311	13/03/2008	24,030,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		112 PTO CAP-1 EXAMEN DE PATENTIBILIDAD	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CLARKE MOSET Y CO. COLOMBIA	CONSIGNACION	BANCO DE BOGOTA	002754307	073022	26/03/2008	7,174,000.00

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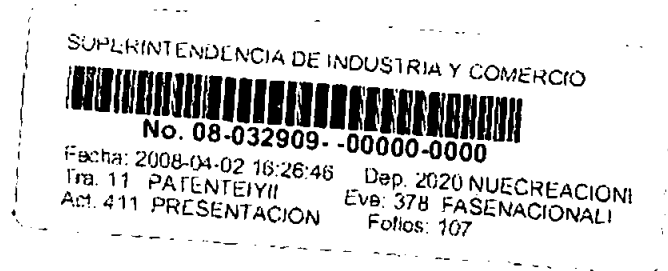
CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005 01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS
			81,000.00
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SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE :

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ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.



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(54) Title: COMBINATION OF POLYCHITOSAMINE AND FIBRATE FOR THE PREVENTION AND TREATMENT OF HYPERLIPIDEMIA

(57) Abstract: The present invention relates to pharmaceutical compositions comprising a fibrate (e.g. ciprofibrate, gemfibrozil, benzfibrate, and fenofibrate) and a polychitosamine (e.g. chitosan) having molecular weights of less than 650 Kda and degrees of deacetylation of from 70% to 100%. Uses of said compositions for the treatment of hyperlipidemia and associated conditions (e.g. hypercholesterolemia, atherosclerosis, coronary heart disease and cardiovascular disease) or as functional foods are also disclosed.

**COMBINATION OF POLYCHITOSAMINE AND FIBRATE FOR THE
PREVENTION AND TREATMENT OF HYPERLIPIDEMIA**

Field of the invention

The present invention relates to the field of therapeutic agents useful in lowering cholesterol or improving the ratio of HLD:LDL (particularly lowering low-density lipoproteins and/or increasing high density lipoproteins) and/or cholesteryl esters, triglycerides, phospholipids and fatty acids in a mammal, such as a human. More particularly, the invention relates to combination therapies, uses, and pharmaceutical compositions having greater therapeutic benefits than monotherapies using the same therapeutic substances.

Background of the invention

It is well known that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol are major risk factors for cardiovascular disease such as atherosclerosis. Numerous studies have demonstrated that a low plasma concentration of high density lipoprotein (HDL) cholesterol (good cholesterol) is a powerful risk factor for the development of atherosclerosis (Barter and Rye, *Atherosclerosis*, 121, 1-12 (1996)). HDL is one of the major classes of lipoproteins that function in the transport of lipids through the blood. The major lipids found associated with HDL include cholesterol, cholesteryl ester, triglycerides, phospholipids and fatty acids. The other classes of lipoproteins found in the blood are low density lipoprotein (LDL), intermediate density lipoprotein (IDL), and very low density lipoprotein (VLDL). Since low levels of HDL cholesterol increase the risk of atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of cardiovascular diseases such as atherosclerosis. Cardiovascular diseases include, but are not limited to, coronary heart disease, peripheral vascular disease, and stroke.

An approach for addressing hyperlipidemia has been the use of polychitosamine, a substance derived from the shell of crustaceans. Polychitosamine is a highly deacetylated and low molecular weight derivative of chitin. As described in Canadian patent no. 2,085,292, enzymatic treatment of chitosan with a hydrolase enzyme results in chitosan derivatives having a decreased molecular weight, decreased viscosity and increased solubility of chitosan in water.

In its mechanism of action, polychitosamine contains free amine groups which attach themselves to lipids such as cholesterol via ionic bonds while in the intestinal tractus, forming an indissociable complex that is eventually excreted. Polychitosamine therefore prevents lipids such as cholesterol from ever entering the bloodstream and adding to the total cholesterol content. It is commonly used in dosages of 400-800mg/three times a day, with meals and is indicated towards the obtention of a healthy lipid profile and more particularly a healthy cholesterol profile. Polychitosamine is well tolerated by patients. Reported side-effects at the dosage levels indicated above have been mild to none. (Veneroni G, Veneroni F, Contos S et al. *Effect of a new chitosan dietary integrator and hypocaloric diet on hyperlipidemia and overweight in obese patients*. Acta Toxicol the 1996 17(1):53-60).

Polychitosamine is currently marketed by Magistral Biotech under the brand names Libracol® (HEP-30) in 800mg gelatine capsules.

Another known therapy is the use of fibrate for lowering blood cholesterol. Fibrates are cholesterol-lowering drugs that are primarily effective in lowering triglycerides and, to a lesser extent, in increasing HDL-cholesterol levels. Several fibrate drugs are commercially available such as Gemfibrozil available under the brand name LOPID. LOPID is the most widely used fibrate in the United States and can be very effective for patients with triglyceride levels. However, it is not very effective for lowering the LDL-cholesterol. As a result, it is used less often than other

drugs and patients with heart disease for whom LDL-cholesterol lowering is the main goal of treatment. It should also be noted that Gemfibrozil as a monotherapy is not recommended by the United States Food and Drug Administration for patients with heart disease.

5

On the other hand, fibrates are generally well-tolerated by most patients. Gastro-intestinal complaints are the most common side effects and fibrates appear to increase the likelihood of developing cholesterol gallstones. Fibrate can increase the effective medications that thin the blood. Fibrates are usually given in two daily doses, 30 minutes before the morning and evening meals. The reductions in triglycerides generally are in the range of 20% to 50% with increase in HDL-cholesterol of 10% to 15%. Other fibrate drugs include Stiprofibrate; Bezafibrate; and Flnofibrate.

15

Another well-known therapeutic approach for treating or preventing hyperlipidemic conditions is the use of HMG-CoA reductase inhibitors (including class of therapeutics commonly called "statins"). Statins are known for reducing blood serum levels of LDL cholesterol by competitive inhibition of the biosynthetic step. Several statins have been developed and commercialized throughout the world. Atorvastatin calcium sold in North America under the brand Lipitor® is a potent reductase inhibitor. However, warning side effects from use of statins include liver dysfunction, skeletal muscle myopathy, rhabdomyolysis and acute renal failure. Some of these effects are exacerbated when statins are taken in greater doses. For example, a patient treated with 10mg per day of Lipitor may notice mild side effects whereas the side effects may greatly increase by simply raising the daily dose to 20mg per day. In fact, on August 8th, 2001, the maker of cerivastatin voluntarily pulled the medicine off the market because of numerous deaths associated with its use. The deaths were caused by complications of severe muscle breakdown.

25

30

A number of combination therapies for the treatment of cardiovascular disease, which include statin as one of the active components, are known. More precisely, the combination therapy of statin and fibrate is well-known. However, recent studies have shown that the risk of developing
5 rhabdomyolysis increases 1400 times when statins are combined with fibrates. This risk is even more prevalent in patients with diabetes who combine these two types of medications, producing as many as 1 in 500 people affected with rhabdomyolysis (<http://www.wnbc.com/dmaxgomez/393553/details.html>).

10

Another example of a combination therapy of fluvastatin and nicotrol is described by J. Sasaki et al. (Int. J. Clin. Pharmacol. Ther., July; 33(7), 420-6 (1995)). Those researchers conclude that the combination of fluvastatin with nicotrol "a dose of 750mg/day does not appear to
15 augment or attenuate beneficial effects of fluvastatin."

L. Cashin-Hemphill et al. (J. Am. Med. Assoc., 264 (23), 3013-17 (1990)) describe beneficial effects of a combination therapy of colestipol and niacin on coronary atherosclerosis.

20

A combination therapy of acipimox and simvastatin shows beneficial effects in patients having high triglyceride levels (N. Hoogerbrugge et al., J. Internal Med., 241, 151-55 (1997)).

25 In a study on the reduction of inflammatory biomarkers by statin, fibrate and combination therapy among diabetic patients with mixed dyslipidemia (G Am Coll Cardiol. 2006 Jul. 18; 48(2):398-401), it has been reported that the anti-inflammatory effects in combination therapies was no more effective than either form of monotherapy.

30

Thus, there is a need for seeking alternative cholesterol lowering strategies that are safe and do not present side effects severe enough to create additional health problems such as rhabdomyolysis. More

particularly, there is a need to provide new therapeutic approaches having the advantages afforded by combination therapies (complementary mode of action) all the while being safe and efficient. The present invention provides such new therapeutic approach in the form of new combinations of cholesterol-lowering agents that are compatible, thus safe to use all the while being at least as effective as the corresponding monotherapies for each of the corresponding cholesterol-lowering agents present in the combination.

10 **Summary of the Invention**

An embodiment of the present invention provides a pharmaceutical composition comprising: a) a pharmaceutically effective amount of fibrate; b) a pharmaceutically effective amount of polychitosamine and optionally c) a pharmaceutically acceptable carrier.

15

An embodiment of the present invention also provides the use of the above-defined pharmaceutical composition to increase the level of HDL in the blood of a mammal.

20

A further embodiment of the present invention provided the use of the above-defined pharmaceutical composition to lower the level of low density lipoproteins in the blood of a mammal.

25

A further embodiment of the present invention provides a method for lowering the concentration of low density lipoprotein in the blood of a mammal and/or improving the ratio of HDL:LDL in such a mammal by increasing the level of high density lipoproteins; the method comprising the step of administering a pharmaceutical composition of the invention or a) a first amount of a fibrate and b) a second amount of polychitosamine; wherein the first and second amounts together comprise a therapeutically effective amount.

30

Another embodiment provides a method for the prophylaxis or treatment of hyperlipidemia or hyperlipidemia-associated condition comprising administering to a patient: a) a first amount of a fibrate and b) a second amount of polychitosamine; wherein the first and second amounts together
5 comprise a therapeutically effective amount.

Further embodiment provides a kit for the prophylaxis or treatment of hyperlipidemia or hyperlipidemia-associated condition in a mammal comprising a plurality of daily doses of dosage forms of a fibrate, a plurality
10 of daily doses of dosage forms of polychitosamine together, and treatment or regimen written instructions.

The present invention has the advantage of providing an alternative therapy for lowering blood cholesterol by unexpectedly combining
15 cholesterol-lowering active agents that are compatible in nature. Such combination allows the use of a reduced amount of each of the cholesterol-lowering active agents, thereby reducing side effects.

Detailed description of the invention

20 The present invention provides combination therapies which have a dual cholesterol-lowering mechanism that allows effective cholesterol lowering with reduced side effects as compared to the corresponding monotherapies. When referring to dual cholesterol-lowering mechanism, it is meant, lowering of total blood cholesterol through two distinct
25 physiological modes of action.

The present invention improves efforts for preventing and/or treating hyperlipidemia, such as by reducing serum cholesterol, by providing a combination therapy approach and a novel pharmaceutical composition
30 that provides therapeutic benefits such as safety and reduced side effects not available through other known mono or multiple therapies for hyperlipidemia. The present invention provides benefits afforded by fibrate in a combination therapy that would be otherwise contraindicated if used in

combination with other known cholesterol-lowering agents such as statin. The polychitosamine/fibrate combination of the present invention allows a patient to benefit from the complementary dual cholesterol-lowering effects of each of these agents without adverse effects caused by incompatibility of the two agents. The invention thus lies in the new combination of polychitosamine and fibrate as a safe and efficient therapy for lowering blood cholesterol.

The present invention provides a combination therapy for lowering blood cholesterol which comprises a combination of at least one fibrate and one polychitosamine. Preferably, the fibrate is selected from the group consisting of ciprofibrate, gemfibrozil, benzaifibrate, and fenofibrate. Also preferably, the polychitosamine is a chitosan salt having a molecular weight of less than about 650 kDa and has a deacetylation degree of about 70% to 100%.

The present invention also provides a method for lowering blood cholesterol and/or increasing the HDL/LDL ratio by increasing the level of HDL by administering to a mammal the pharmaceutical composition of the present invention or by administering a composition comprising an effective amount of fibrate and polychitosamine.

The present invention also provides a method for the prophylaxis or treatment of hyperlipidemia or hyperlipidemia associated condition comprising administering to a patient the pharmaceutical composition of the present invention or a composition comprising an effective amount of at least a fibrate or polychitosamine.

The present invention further provides an oral dosage form of a pharmaceutical composition comprising a combination of polychitosamine and fibrate wherein the dosage form provides to a mammal in need of treatment by the polychitosamine and fibrate, a therapeutically effective

dose of polychitosamine and therapeutically effective quantity of fibrate into the blood of said mammal.

5 The present invention also provides a kit for the prophylaxis or treatment of hyperlipidemia in a mammal, the kit comprising a plurality of daily doses of dosage forms of a fibrate and a polychitosamine together with a treatment regimen instructions.

10 The combinations of the present invention will have a number of advantages. For example, through dosage adjustment and medical monitoring, the individual dosages of the therapeutic compounds used in the combinations of the present invention will be lower than the typical dosages of the therapeutic compounds when used in monotherapy. The dosage lowering will provide advantages including reduction of side effects
15 of the individual therapeutic compounds when compared to the monotherapy. In addition, fewer side effects of the combination therapy compared with the monotherapies will lead to greater patient compliance with therapy regimens.

20 Another advantage provided by the combination therapy of the present invention is that it provides a dual cholesterol-lowering mechanism that consists of complementary effects or complementary modes of action for lowering blood cholesterol. For example, fibrate can control blood serum cholesterol levels by decreasing serum triglycerides via reduced hepatic
25 production and increased triglyceride clearance by the peripheral tissues and increase HDL. In contrast, polychitosamine can block the migration of cholesterol and/or other lipids such as cholesteryl esters and triglycerides from the intestinal tractus to the blood stream, and the reabsorption of bile acids from the intestinal tractus to the blood stream.

30 A further advantage of the combination therapy provided by the present invention is that it is safe to use due to the very low incidence of side effects or adverse events caused by the combination of same. In the

present case, the fibrate is combined with a polychitosamine which is a natural occurring biopolymer which is also known to be useful in lowering blood cholesterol. As previously indicated, polychitosamine is currently marketed by Magistral as a dietary supplement under the brand Libracol® (HEP 30) in 800ml gelatin capsules.

Definitions

As used herein the term "fibrate" refers to a class of amphipathic carboxylic acids. They are used for a range of metabolic disorders mainly hypercholesterolemia (high cholesterol), hyperlipidemia and are therefore hyperlipidemic agents.

As used herein, "chitin" refers to a polymer formed primarily of repeating units of β (1-4) 2-acetamido-2-deoxy-D-glucose (or N-acetylglucosamine). Not every unit of naturally-occurring chitin is acetylated, with about 16% deacetylation.

As used herein, "chitosan" refers to chitin that has been partially or fully deacetylated. Chitosan is a polysaccharide formed primarily of repeating units of β (1-4) 2-amino-2-deoxy-D-glucose (or D-glucosamine). Further deacetylation of chitin can be achieved by processing of chitin. Deacetylation values can vary with chitin sources and with processing methods.

As used herein the term "polychitosamine" or the term "chitodextrine", refers to a chitosan polymer having a molecular weight of less than about 650 kDa, preferably about 2-500 kDa, more preferably about 15-200 kDa, still more preferably about 20-100 kDa, yet more preferably about 25-60 kDa, and ideally about 30-50 kDa. In one embodiment, the molecular weight of the polychitosamine is about 30 kDa and in another embodiment, the molecular weight is about 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 kDa. The polychitosamine can be obtained by cleaving a heavier molecular chain of

chitosan. Preferably, polychitosamine is highly deacetylated, such as over about 80%, and more preferably over about 89%. Polychitosamine is understood herein to also encompass a chitosan salt formed from any chitosan molecule associated with a negatively charged anion. A series of
5 anions has been used for that purpose. For example, anions derived from inorganic acids such as sulphuric acid (sulphate), phosphoric acid (phosphate), hydrochloric acid (chloride) and organic acids such as malic acid (malate), tartaric acid (tartrate), citric acid (citrate), succinic acid (succinate) and lactic acid (lactate), chitin, chitosan, and their derivatives.

10

As used herein the term "combination therapy" refers to the administration of two or more therapeutic agents to treat a hyperlipidemic condition, for example atherosclerosis and hypercholesterolemia. Such administration encompasses co-administration of these therapeutic agents in a
15 substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate dosage forms for each type of therapeutic agent in a sequential or staggered manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the hyperlipidemic condition.

20

As used herein, "nutraceuticals" is understood to encompass any ordinary food that has components or ingredients added to give a specific medical or physiological benefit other than a purely nutritional effect. It is also understood to include functional foods, dietary supplements and over the
25 counter products sold without a prescription.

As used herein, "functional foods" is understood to encompass any food consumed as part of a usual diet that is similar in appearance to, or may be, a conventional food, and is demonstrated to have physiological
30 benefits and/or reduce the risk of chronic disease beyond basic nutritional functions.

The phrase "therapeutically effective" is intended to qualify the amount of the active ingredient in the combination therapy that will achieve the goal of reducing or eliminating the hyperlipidemic condition.

- 5 The phrase "therapeutic compound" refers to a compound useful in the prophylaxis or treatment of a hyperlipidemic condition, such as, but not limited to, atherosclerosis, hypercholesterolemia, coronary heart disease, and cardiovascular disease.
- 10 The phrase «pharmaceutically effective» is intended to qualify the amount of the ingredient that will achieve the goal intended by the pharmaceutical composition.

- 15 The phrase «dual cholesterol-lowering mechanism» means lowering of total blood cholesterol through two distinct physiological modes of action.

Polychitosamine

- Polychitosamine refers to a chitosan polymer having a molecular weight of less than about 650 kDa, preferably about 2-500 kDa, more preferably about 15-200 kDa, still more preferably about 20-100 kDa, yet more preferably about 25-80 kDa, and ideally about 30-50 kDa.
- 20

- Chitosan is a naturally-occurring biopolymer that can also be obtained by partial or complete deacetylation of chitin that is the major component of the exoskeleton of shellfishes and insects. Chitosan is therefore a linear polymer composed of monomers of *N*-acetyl-2-amino- β -D-glucose and 2-amino- β -D-glucose. The presence of the primary amino groups of the 2-amino- β -D-glucose (*D*-glucosamine) units confers to chitosan its polycationic (positively charged) character that is neutralized by accompanying negatively charged anions. A series of anions has been used for that purpose. For example, anions derived from inorganic acids such as sulfuric acid (sulfate), phosphoric acid (phosphate), hydrochloric acid (chloride), and a mixture thereof and organic acids such as malic acid
- 25
- 30

(malate), tartaric acid (tartrate), citric acid (citrate), lactic acid (lactate), acetic acid (acetate), formic acid (formate), glycolic acid (glycolate), oxalic acid, succinic acid, ascorbic acid, maleic acid, acrylic acid, gluconic acid, glutamic acid, propionic acid and a mixture thereof have been reported as salts of chitosan.

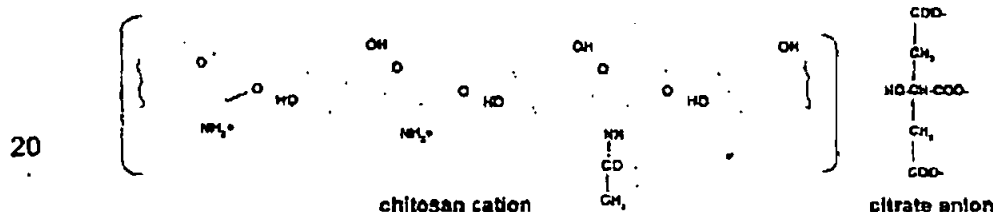
While there exists many extraction methods of the chitin from the crustacean shells, the principles of chitin extraction are relatively simple. In a certain treatment, the proteins are removed in a dilute solution of sodium hydroxide (such as about 1%-10%) at high temperature (such as about 85°C-100°C). Shells are then demineralized to remove calcium carbonate. This can be done by treating in a dilute solution of hydrochloric acid (1%-10%) at room temperature. Depending on the severity of these treatments such as temperature, duration, concentration of the chemicals, concentration and size of the crushed shells, the physico-chemical characteristics of the extracted chitin can vary. For instance, three characteristics of the chitin, such as the degree of polymerization, acetylation, and purity, can be affected. Shell also contains lipids and pigments. Therefore, a decolorizing step is sometimes needed to obtain a white chitin. This can be done by soaking in organic solvents or in a very dilute solution of sodium hypochlorite. Again, these treatments can influence the characteristics of the chitin molecule.

Chitin can be deacetylated partially or totally. Such a deacetylated polymer is called chitosan. Chitosan compounds in a range of up to and exceeding 1×10^6 molecular weight are derived commercially from chitin. In nature, chitosan is present in cell walls of Zygomycetes, a group of phytopathogenic fungi. Because of its significant content of free amino groups, chitosan has a markedly cationic character and has a positive charge at most pHs. Canadian Patent 2,085,292 discloses the hydrolysis of chitosan, the disclosure of which is incorporated herein by reference.

Polychitosamine can be produced by the process described in Canadian Patent 2,085,292, and recovered from solution using the process described in WO 2005/068213-A1 where the chitosan is salted out with a salting-out salt such as but not limited to sulfates, phosphates, citrates, nitrates, malates, tartrates, succinates, propionates, lactates and hydrogen phosphates. More preferably, these salting-out salts may be selected from the group consisting of: ammonium or sodium sulfate; sodium or potassium phosphates; sodium or potassium citrate; sodium tartrate; sodium malate; sodium nitrate; sodium lactate; sodium malonate; sodium succinate; sodium acetate; sodium propionate. Thus, the present invention includes any chitosan derivative obtained by any of the above-mentioned salts.

As an example, the citrate salt of chitosan can be illustrated as follows:

15



polychitosamine.

25 In a mechanism of action, polychitosamine, in particular chitosan, can contain free amine groups which can attach themselves to lipids, such as cholesterol, via ionic bonds while in the intestinal tractus, forming an indissociable complex which is eventually excreted. Polychitosamine therefore can prevent lipids, such as cholesterol, from ever entering the bloodstream and adding to the total cholesterol content. Also, in reaction, the liver eliminates more cholesterol by using biliary acids. Therefore, there is elimination of both food cholesterol and that of biliary acids rich in cholesterol.

35 Molecular Weight

Polychitosamine has many potential applications depending on its molecular weight. An average high molecular weight polychitosamine is about 650 kDa. Some applications are typical of medium or low molecular weight polychitosamine, ranging typically about 2-500 kDa. These applications include its use as an antifungal agent; a seed coating for improving crop yield; an elicitor of anti-pathogenic natural reactions in plants; a hypocholesterolemic agent in animals; an accelerator of lactic acid bacteria in breeding; and a moisture-retaining agent for lotions, hair tonics and other cosmetics.

10

The molecular weight of polychitosamine is a feature that is particular to a certain application. The molecular weight of the native chitin has been reported to be as high as many million Daltons. However, chemical treatment tends to bring down the molecular weight of the polychitosamine, ranging from 100 kDa to 1500 kDa. Further treatment of the polychitosamine can lower the molecular weight even more. Low molecular weight could be produced by different ways including enzymatic or chemical methods. When the chain becomes shorter, the polychitosamine can be dissolved directly in water without the need of an acid. This is particularly useful for specific applications, such as in cosmetics or in medicine. Molecular weight of the polychitosamine can be measured by analytical methods, such as gel permeation chromatography, light scattering, or viscometry. Because of simplicity, viscometry is the most commonly used method.

25

In one embodiment, the molecular weight of the polychitosamine is about 30 kDa and in another embodiment, the molecular weight is about 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 kDa. The polychitosamine can be obtained by cleaving a heavier molecular chain of chitosan.

30

Deacetylation

Chitin can be deacetylated partially or totally. Naturally occurring chitin is acetylated, with about 16% deacetylation. Chitosan refers to chitin that has been partially or fully deacetylated. Chitosan is a polysaccharide formed primarily of repeating units of β (1-4) 2-amino-2-deoxy-D-glucose (or D-glucosamine). Further deacetylation of chitin can be achieved by processing of chitin. Deacetylation values can vary with chitin sources and with processing methods.

Since chitosan is made by deacetylation of chitin, the term degree of deacetylation (DAC) can be used to characterize chitosan. This value gives the proportion of monomeric units of which the acetylic groups that have been removed, indicating the proportion of free amino groups (reactive after dissolution in weak acid) on the polymer. DAC could vary from about 70% to about 100%, depending on the manufacturing method used. This parameter indicates the cationic charge of the molecule after dissolution in a weak acid. There are many methods of DAC measurements, such as UV and infrared spectroscopy, acid-base titration, nuclear magnetic resonance, dye absorption, and the like. Since there are no official standard methods, numbers tend to be different for different methods. In high value product, NMR can give a precise DAC number. However, titration or dye absorption can serve as a quick and convenient method and yield similar results as NMR.

Chitin deacetylation towards chitosan can be obtained by various methods. The most used method is that of alkaline treatment (Horowitz, S. T. et al., 1957). With this method, around 80% of deacetylation can be achieved without significant decrease of molecular weight. A more intense deacetylation cannot be obtained by this method without a simultaneous uncontrolled decrease of the degree of polymerization. A more promising method is deacetylation by a thermo-mechano-chemical treatment (Pelletier et al., 1990). This method allows a more careful control of the various characteristics of the final product (average degree of

polymerization and of deacetylation). Finally, a third method (Domard and Rinaudo, 1983) allows obtainment of a totally deacetylated product.

5 In a certain deacetylation protocol, when chitin is heated in a basic solution, such as a strong solution of sodium hydroxide (such as about 40%) at high temperature (such as about 90°C-120°C), chitosan is formed by deacetylation. This treatment can remove acetylic grouping on the amine radicals to a product (chitosan) that could be dissolved. It is said that at least 65% of the acetylic groups should be removed on each
10 monomeric chitin to obtain the ability of being put in solution. The degree of deacetylation will vary according to the treatment conditions, such as the duration, the temperature and the concentration of the basic solution.

In the preferred embodiments, the polychitosamine has a deacetylation
15 higher than about 80%. Preferably, the polychitosamine has a deacetylation higher than about 89%. More preferably, the polychitosamine has a deacetylation higher than about 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%. In a polychitosamine that has been deacetylated about 100%, the advantage being the polychitosamine forms
20 a relatively homogeneous composition.

According to the present invention, the polychitosamine has a molecular weight of about 30 kDa and is deacetylated at least 80%. In a preferred
25 embodiment, the polychitosamine has a molecular weight of about 30 kDa and is deacetylated at least 93% and is sold under the trademark Libracol® in Canada.

Fibrate

30 Fibrates are a class of amphipathic carboxylic acids. Their main actions are to decrease serum triglycerides and increase HDL. They act via activation of peroxysome proliferator-activated receptors (PPAR) α that are involved in the regulation of a number of genes involved in lipid metabolism. Fibrates are also effective at reducing the circulating

concentration of small dense LDL. In an embodiment of the present invention, the fibrate is selected from the group consisting of ciprofibrate; gemfibrozil; bezafibrate; and fenofibrate. Preferably, fenofibrate is used in the combination therapy of the present invention.

5

Synergism

Synergy or synergism, most often refers to the phenomenon of two or more discrete influences or agents acting in common to create an effect which is greater than the sum of the effects each is able to create independently.

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Warnings of side effects from use of fibrate include renal impairment, severe hepatic impairment, hypoalbuminaemia, primary biliary cirrhosis, gallbladder disease, and nephrotic syndrome. Some of these effects are noted when fibrate is taken in regular doses of at least about 1200mg per day.

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Accordingly, an advantage of using drug synergism is the ability to use a reduced amount of fibrate for the same result as in fibrate monotherapy, thus, resulting in fewer side effects.

20

Prevention and Treatment of Conditions

The preferred embodiments can be used to prevent, give relief from, or ameliorate a disease condition having hyperlipidemia as an element of a disease, such as atherosclerosis or coronary heart disease, or to protect against or treat further high cholesterol plasma or blood levels with the compounds and/or compositions of the preferred embodiments. Hyperlipidemia is an elevation of lipids (fats) in the bloodstream. These lipids include cholesterol, cholesterol esters (compounds), phospholipids, triglycerides, and fatty acids. These lipids are transported in the blood as part of large molecules called lipoproteins.

25

30

Adverse events of hyperlipidemia include atherosclerosis and coronary heart disease. Atherosclerosis is a disease characterized by the deposition of lipids, including cholesterol, in the arterial vessel wall, resulting in a narrowing of the vessel passages and ultimately hardening the vascular system. The primary cause of coronary heart disease (CHD) is atherosclerosis. CHD occurs when the arteries that supply blood to the heart muscle (coronary arteries) become hardened and narrowed. As a result of CHD, there could be angina or heart attack. Over time, CHD can weaken your heart muscle and contribute to heart failure or arrhythmias.

10

Hypercholesterolemia is also linked to cardiovascular disease. Cardiovascular disease refers to diseases of the heart and diseases of the blood vessel system (arteries, capillaries, veins) within a person's entire body, such as the brain, legs, and lungs. Cardiovascular diseases include, but are not limited to, coronary heart disease, peripheral vascular disease, and stroke.

15

Accordingly, an embodiment of the present invention relates to the use of the combination therapy of polychitosamine and fibrate for lowering blood cholesterol in a mammal. Preferably, the mammal is a human.

20

Accordingly, another embodiment of the present invention relates to the use of the combination therapy of polychitosamine and fibrate in the prevention or treatment of hyperlipidemia and conditions associated with hyperlipidemia, such as hypercholesterolemia, atherosclerosis, coronary heart disease, and cardiovascular disease.

25

It should be understood that the combination therapy of polychitosamine and fibrate as mentioned hereinabove may be in the form of a pharmaceutical composition according to the present invention or any other composition comprising a combination of polychitosamine and fibrate. In the case of such composition, the nature and amount of polychitosamine and fibrate may be similar to those specified in the

30

pharmaceutical composition of the present invention. A person skilled in the art could easily determine the exact amount based on the information provided in the instant application.

5 Pharmaceutical Compositions

The compounds useful in the preferred embodiments can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier is acceptable in the sense of being compatible with the other ingredients of the composition and is not deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a capsule or tablet, which can contain from about 0.05% to about 95% by weight of the active compound. Examples of suitable carriers, diluents, and excipients include, but are not limited to, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, alginates, tragacanth, gelatin, calcium silicate, cellulose, magnesium carbonate, or a phospholipid with which the polymer can form a micelle. Other pharmacologically active substances can also be present, including other compounds of the preferred embodiments. For example, more than one fibrate may be used together. The pharmaceutical compositions of the preferred embodiments can be prepared by any of the well-known techniques of pharmacy, comprising admixing the components.

25 In practicing the methods of the preferred embodiments, administration of the fibrate, in combination therapy, may be accomplished by oral route.

For oral administration, compounds used in the combination therapy can be in the form of, for example, but not limited to, a tablet, capsule, suspension, powders (e.g., for sprinkling on food), or liquid. Other embodiments include sustained-release capsules, enteric coated tablets, soft gel capsules, and other sustained-release technologies. Capsules, tablets, liquid, or powders, and the like can be prepared by conventional methods well-known in the art. The compounds are preferably made in

the form of a dosage unit containing a specified amount of the compound. Examples of dosage units are tablets or capsules.

5 Pharmaceutical compositions for use in the treatment methods of the preferred embodiments can be administered in oral form for compounds of the composition, or by parenteral, such as intravenous administration for the fibrate and oral administration of the polychitosamine. For convenience, oral administration of both therapeutic substances is preferred. Dosing for oral administration can be with a regimen calling for
10 single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the day.

Nutraceuticals

15 The compounds useful in the present invention can be incorporated in a functional food or nutraceutical. These compounds may be presented in the form of active agents such as cholesterol lowering agents. As such, these compounds may be useful in the manufacture of nutraceuticals and/or functional foods useful for preventing hyperlipidemia associated conditions.

20 In a preferred embodiment, the polychitosamine and fibrate compounds are incorporated in functional foods including but not limited to: beverages, including but not limited to sodas, water, sports/energy drinks, canned and bottled juices, fresh and refrigerated juices, frozen juices, yoghurt drinks, smoothies, teas and coffees; breads and grains, including but not limited
25 to breakfast cereals, breads, baked goods, baking ingredients such as flour, frozen breads, dried breads and crackers, pastas; snack foods, including but not limited to nutrition bars, weight loss bars, energy/sports bars, candy bars, chips, gum; packaged and prepared foods, including but
30 not limited to frozen foods such as pizzas and dinners, canned and dried soups, desserts including cookies; condiments, including but not limited to dressings, spreads, sauces; dairy and dairy alternatives, including but not limited to milk, cheese, butter, ice cream, yoghurt, margarine and soymilk.

Dosages

A total daily dose of fibrate can generally be in the range of from about 50mg/day to about 1200mg/day in single or divided doses. Certain
5 embodiments, with regard to appropriate dosage, are shown in Table I.

Table I

FREQUENCY OF ADMINISTRATION	DOSAGE PER ADMINISTRATION						
	HEP	Ciprofibrate	Fenofibrate	Kenofibrate (Lipidi micro)	Finofibrate (Lipidi Supra)	Gemfibrozil	Benzafibrate
Once per day (1 to 3 capsules)	600 to 2,400 mg	50 to 100 mg	60 to 300 mg	70 to 300 mg	80 to 200 mg	600 to 1200 mg	200 to 400 mg
Per capsule	200 to 600 mg	16 to 100 mg	18 to 300 mg	23 to 300 mg	16 to 200 mg	200 to 600 mg	66 to 400 mg
Twice per day (1 to 2 capsules per)	400 to 1,200 mg	25 to 60 mg	25 to 150 mg	38 to 150 mg	25 to 100 mg	300 to 600 mg	100 to 200 mg
Per capsule	200 to 600 mg	12.5 to 50 mg	12.5 to 150 mg	18 to 150 mg	12.5 to 100 mg	150 to 600 mg	50 to 200 mg

In the case of pharmaceutically acceptable fibrate salts, the weights
10 indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

For a polychitosamine, a total daily dose of about 400mg to about 4.8 grams per day and preferably between about 800mg and about 2.4 grams
15 per day may generally be appropriate. In an embodiment, polychitosamine is administered at about 400mg per day. The polychitosamine is preferably taken three times a day. The polychitosamine is preferably taken with meals.

20 Certain Dosages

As used herein, the term "total daily dose" refers to the amount of composition administered to an individual in one day.

The term "dose" refers to the amount of composition administered to an
25 individual at one time.

The term "unit dose" refers to the amount of a composition pre-packaged by the manufacturer or pharmacist in standardized amounts. Thus, for example, the dose of ingredients in a single tablet or capsule would be considered a single "unit dose" whether one or more tablets or capsules are taken simultaneously.

In another embodiment, a polychitosamine is administered with a total daily dose of about 600mg to about 2400mg and a fibrate is administered at a total daily dose of about 50mg to about 1200mg. Preferably, the total daily dose is administered once per day in about 1 to about 3 unit doses, preferably in capsule form. Accordingly, each unit dose may contain about 200mg to about 1200mg of polychitosamine. Also, each unit dose may contain about 16mg to about 600mg of fibrate. In an embodiment, the total daily dose is administered in two unit doses administered once a day; the unit dose containing about 600mg of polychitosamine and at least about 50mg of fibrate. The dose is preferably administered with meals.

In another embodiment, the total daily dose is administered in two doses per day. In each dose, there is a polychitosamine in an amount of about 200mg to about 1200mg and a fibrate in an amount of about 50mg to about 40mg. Preferably, the total daily dose is administered in two doses per day with about 1 to about 2 unit doses per dose. Accordingly, each unit dose may contain about 200mg to about 600mg of polychitosamine. Also, each unit dose may contain about 25mg to about 600mg of fibrate. In an embodiment, the unit dose is administered in one capsule administered twice a day; the unit dose containing about 600mg of polychitosamine and about 50mg of fibrate. The dose is preferably administered with meals.

The dosage regimen to treat hyperlipidemia and hyperlipidemia-associated conditions, and reduce plasma cholesterol with the combination therapy and pharmaceutical compositions of the preferred embodiments is selected in accordance with a variety of factors. These factors include, but

are not limited to, the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

Initial treatment of a patient suffering from a hyperlipidemic condition, such as, but not limited to, hypercholesterolemia, atherosclerosis, coronary heart disease, and cardiovascular disease, can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the condition has been controlled or eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for example, measuring serum LDL and total cholesterol levels by any of the methods well known in the art, to determine the effectiveness of the combination therapy.

Kits

The preferred embodiments also relate to kits for conveniently dispensing the combination therapy. These kits will preferably contain a plurality of daily doses of the fibrate and of the polychitosamine. The daily doses are preferably separate dosage forms of each medicament. Instructions are also provided for patient and/or dispensing physician or pharmacist. The kits may contain supplies for a given time duration of treatment such as one month.

Blister package with 7 days worth of treatment, each day indicated (Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday). Each day has two capsules or tablets, one indicated as "breakfast", the other indicated as "supper". There are a total of 14 capsules per blister

pack (2 rows and 7 columns) and four blisters in a box – enough for a four week (28 days) supply. Alternatively, you could have one single row for once daily dosing (dinner only), or three rows for three times per day dosing (breakfast, lunch, dinner). According to this embodiment, the fibrate and the polychitosamine are contained in the same capsule or tablet.

According to another embodiment, the fibrate and the polychitosamine are in separate tablets or capsules, one dose per day of each, for each of seven days. This would represent 2 rows and 7 columns per blister, with 4 blisters per box.

Those skilled in the art will know, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. These and all other equivalents are intended to be encompassed by the following claims.

Although the present invention has been explained hereinabove by way of a preferred embodiment thereof, it should be pointed out that any modifications to this preferred embodiment within the scope of the appended claims is not deemed to alter or change the nature and scope of the present invention.

Example 1

1.0 SUMMARY OF THE TRIAL

<i>Name of product studied</i>	HEP-40 TM (40 kDa, 93% deacetylated, polychitosamine)
<i>Trial title</i>	A 12 week, double blind, placebo controlled, randomized pilot study evaluating the effectiveness of HEP-40 TM co-administered with a fibrate in patients with persistent hypercholesterolemia while on fibrate monotherapy.
<i>Estimated trial start & duration</i>	Treatment: 12 weeks.

Hypotheses	Primary: In patients with persistent hypercholesterolemia defined as above target LDL-C while on fibrate monotherapy, a 12 week course of 800mg bid of HEP-40™ co-administered with the current fibrate will produce a significantly higher reduction in circulating serum LDL-C when compared to placebo. Secondary: - In patients with persistent hypercholesterolemia defined as above target LDL-C while on fibrate monotherapy, a 12 week course of 800mg bid of HEP-40™ co-administered with the current fibrate will produce significantly higher reductions in the following lipid parameters when compared to placebo: ▪ Triglycerides. ▪ Total cholesterol ▪ C - Reactive Protein - In patients with persistent hypercholesterolemia defined as above target LDL-C while on fibrate monotherapy, a 12 week course of 800mg bid of HEP-40™ co-administered with the current fibrate will be well tolerated and safe.
Primary objective	In patients with persistent hypercholesterolemia defined as above recommended target LDL-C while on fibrate monotherapy: To compare the effectiveness of a 12 week course of 800mg bid of HEP-40™ versus placebo co-administered with the current fibrate in reducing circulating serum LDL-C.

Secondary objectives	In patients with persistent hypercholesterolemia defined as above recommended target LDL-C while on fibrate monotherapy: - To compare the effectiveness of 800mg bid of HEP-40™ versus placebo co-administered with the current fibrate at an unaltered dose in reducing the following lipid parameters: ▪ Triglycerides. ▪ Total cholesterol ▪ C – Reactive Protein - To assess the safety and tolerability of a 12 week course of 800mg bid of HEP-40™ co-administered with the current fibrate.
Clinical phase	Phase IV Pilot Study
Trial design	Double blind, placebo controlled, randomized trial Patients with persistent hyperlipidemia, defined as LDL-C levels above recommended target while on fibrate monotherapy will be enrolled. Patients must be on fibrate therapy for more than 4 weeks but less than 6 months. Patients will be randomized in a 1:1 ratio to be treated with: ▪ HEP-40 at 800mg bid co-administered with their current fibrate for 12 weeks (HEP-40) ▪ placebo bid co-administered with their current fibrate for 12 weeks (PLACEBO)
Number of patients to be included	At least 20 patients will be enrolled and randomized. At least 14 evaluable patients are required.
Formulation, route of administration & dosage	Fibrate treatment will continue as per prior to study entry. Study drug (HEP-40 or placebo) will be administered orally during meals. Placebo and HEP- 40 will be similar in formulation, appearance and taste.

Claims

1. A pharmaceutical dosage form comprising in combination:
a) a pharmaceutically effective amount of fibrate;
5 b) a pharmaceutically effective amount of polychitosamine; and
optionally
c) a pharmaceutically acceptable carrier.
2. The dosage form according to claim 1, wherein the polychitosamine
10 has a molecular weight ranging from about 30 kDa to about 50 kDa.
3. The dosage form according to claim 1 or 2, wherein the
polychitosamine has a degree of deacetylation ranging from about 80%
to about 100%.
- 15 4. The dosage form according to claim 3, wherein the polychitosamine
has a molecular weight of about 30 kDa and a degree of deacetylation
of about 89%.
- 20 5. The dosage form according to claim 4, wherein the polychitosamine
is Libracol®.
6. The dosage form according to claim 3, wherein the polychitosamine
has a molecular weight of about 40 kDa and a degree of deacetylation
25 of at least 80%.
7. The dosage form according to any one of claims 1 to 6, wherein the
fibrate is fenofibrate.
- 30 8. The dosage form according to any one of claims 1 to 7, wherein it
comprises at least about 25mg of fibrate per dosage form per day.

9. The dosage form according to any one of claims 1 to 8, wherein it comprises at least 400mg of polychitosamine per dosage form per day.
- 5 10. The dosage form according to any one of claims 1 to 9, for the prevention or treatment of hyperlipidemia and hyperlipidemia-associated condition.
- 10 11. The dosage form according to claim 10, wherein the hyperlipidemia-associated condition is selected from the group consisting of hypercholesterolemia, atherosclerosis, coronary heart disease and cardiovascular disease.
- 15 12. A pharmaceutical composition useful in the prevention or treatment of hyperlipidemia and hypercholesterolemia-associated condition, the pharmaceutical composition comprising at least:
- a pharmaceutically effective amount of fibrate;
 - a pharmaceutically effective amount of polychitosamine; and
 - a pharmaceutically acceptable carrier.
- 20 13. The composition according to claim 12, wherein the polychitosamine has a molecular weight ranging from about 30 kDa to about 50 kDa.
- 25 14. The composition according to claim 12 or 13, wherein the polychitosamine has a degree of deacetylation ranging from about 80% to about 100%.
- 30 15. The composition according to claim 14, wherein the polychitosamine has a molecular weight of about 30 kDa and a degree of deacetylation of about 89%.

16. The composition according to claim 14, wherein the polychitosamine has a molecular weight of about 40 kDa and a degree of deacetylation of at least 80%.

5 17. The composition according to claim 15, wherein the polychitosamine is Libracol®.

18. The composition according to any one of claims 12 to 17, wherein the fibrate is fenofibrate.

10 19. The composition according to any one of claims 12 to 18, wherein the pharmaceutically effective amount of fibrate is at least about 25mg.

15 20. The composition according to any one of claims 12 to 19, wherein the pharmaceutically effective amount of polychitosamine is at least 400mg.

21. The composition according to any one of claims 12 to 20, for the prevention or treatment of hyperlipidemia and hyperlipidemia-associated condition.

22. The composition according to claim 21, wherein the hyperlipidemia-associated condition is selected from the group consisting of hypercholesterolemia, atherosclerosis, coronary heart disease and cardiovascular disease.

23. A method for preventing or treating hyperlipidemia in a mammal comprising administering to said mammal an effective amount of the dosage form of claim 1, or the composition of claim 12.

30 24. The method according to claim 23, wherein the amount of fibrate administered to the mammal is at least about 50mg per day.

25. The method according to claim 23 or 24, wherein the amount of polychitosamine administered to the mammal is at least 600mg per day.
- 5 26. The method according to any one of claims 23 to 25 wherein the mammal is a human.
- 10 27. A method for lowering blood cholesterol in a mammal, wherein said method comprises the step of administering to said mammal an effective amount of the dosage form of claim 1 or the composition of claim 12.
- 15 28. The method according to claim 27 wherein the amount of fibrate administered to the mammal is at least 50mg per day.
- 20 29. The method according to claim 27 or 28 wherein the amount of polychitosamine administered to the mammal is at least 600mg per day.
- 25 30. The method according to any one of claims 27 to 29 wherein the mammal is a human.
31. A functional food comprising an effective amount of polychitosamine and an effective amount of fibrate.
32. The functional food according to claim 31 selected from the group consisting of beverages, bread, grain, snack foods, prepared and packaged foods, condiments and dairy and dairy alternatives.
- 30 33. The functional food according to claim 31 or 32 wherein the polychitosamine has a molecular weight ranging from about 30 kDa to about 50 kDa.

34. The functional food according to any one of claims 31 to 33 wherein the polychitosamine has a degree of deacetylation ranging from about 80% to 100%.
- 5 35. The functional food according to any one of claims 31 to 34 wherein the polychitosamine has a molecular weight of about 30 kDa and a degree of deacetylation of about 89%.
- 10 36. The functional food according to claim 35 wherein the polychitosamine is Libracol®.
37. The dosage form according to any one of claims 31 to 36 wherein the fibrate is fenofibrate.
- 15 38. The functional food according to any one of claims 31 to 37 wherein it comprises at least about 25mg of fibrate.
39. The functional food according to claim 38 wherein it comprises at least 400mg of polychitosamine.
- 20 40. A kit for the prophylaxis or treatment of hyperlipidemia in a mammal, the kit comprising a plurality of daily doses of dosage forms of a fibrate and a polychitosamine together with a treatment regimen instructions.
- 25 41. The kit according to claim 40, wherein the daily dose of fibrate is at least 50mg per day.
- 30 42. The kit according to claim 41, wherein the daily dose of polychitosamine is at least 600mg per day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001603

A. CLASSIFICATION OF SUBJECT MATTER

IPC: *A61K 31/7008* (2006.01), *A61K 31/216* (2006.01), *A23L 1/30* (2006.01), *A61K 31/722* (2006.01), *A61P 3/06* (2006.01).

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/7008 (2006.01), *A61K 31/216* (2006.01), *A23L 1/30* (2006.01), *A61K 31/722* (2006.01), *A61P 3/06* (2006.01).Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
*A61K*Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Delphion, CPD, Scopus, Pubmed; fibrate, ciprofibrate, gemfibrozil, bezafibrate, fenofibrate; polychitosamine, chitosan, heparin, acetyl-gingecamine; hyperlipidemia, hypercholesterolemia, atherosclerosis, coronary, cardio.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<i>Martinac et al.</i> Dec 2002 (12-2002) Eur. J. of Pharm. Sci., Vol. 17 (4-5), pp. 207 - 216.	1, 3, 4, 8 - 12, 14, 19 - 30, 40 - 42
Y	<i>Gemfibrozil encapsulation and release from microspheres and macromolecular conjugates.</i> D1: See entire article, especially pages 207 and 208.	7, 18
X	<i>Remuñán-López et al.</i> 1995 (1995) Proceed. Intern. Symp. Control. Rel. Bioact. Mater., Vol 22, pp. 430 - 431. <i>Development of new chitosan-gelatin microcapsules produced by a complex coacervation process.</i> D2: See entire article.	1
X	<i>Jorgensen et al.</i> WO 98/22114 25 May 1998 (28-05-1998) <i>A method of promoting tissue repair.</i> D3: See page 37 and 76.	1

☒ Further documents are listed in the continuation of Box☒ See patent family annex

Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"B"	earlier application or patent but published on or after the international filing date
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"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and put in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"Z"	document member of the same patent family

Date of the actual completion of the international search

8 December 2006 (08-12-2006)

Date of mailing of the international search report

18 January 2007 (18-01-2007)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Ottawa, Quebec K1A 0G9
Facsimile No.: 001(819)953-2476

Authorized officer

C. Bourque 819-934-3596

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001603

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim 23 - 30

because they relate to subject matter not required to be searched by this Authority, namely :

The subject matter of claims 23 - 30 relate to methods of medical treatment of the human or animal body (Rule 39.1(iv) of the PCT). For the assessment of these claims with respect to their industrial applicability (Article 33(4) of the PCT), no unified criteria exists in the PCT. The patentability of the subject matter defined by these claims in the different member states may depend on the formulation of these claims. Certain national offices accept claims worded as methods of medical treatment, while other offices accept claims worded as use claims. Accordingly, search has been established with regard to the alleged effects or purposes/uses of the compounds defined in claims 23 - 30.

2. ☐ Claim

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. ☐ Claim

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/001603

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant	Relevant to claim No.
Y	Merck Index. 11th ed. 1989 (1989) Entry 3924, pp. 624 - 625. <i>Fenofibrate.</i> D4: See entire entry.	7, 18
A	Hardinge-Lyme, N. CA 2,339,125 10 Feb 2000 (10-02-2000) <i>Novel chitosan-containing liquid compositions and methods for their preparation and use.</i> D5: See entire document.	1 - 42
A	Ryde et al. CA 2,487,054 23 Nov 2004 (23-11-2004) <i>Nanoparticulate fibrate formulations.</i> D6: See entire document.	1 - 42

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2006/001603

Patent Document Cited in Search Report	Date	Publication Member(s)	Patent Family Date	Publication Date
WO9822114	28-03-1998	AU4941297 A	10-06-1998	
CA2339125	10-02-2000	AT268124T T	15-06-2004	
		AU747611B B2	16-05-2002	
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		WO2004041250 A2	21-05-2004	

**COMBINACIÓN DE POLIGLUCOSAMINA Y FIBRATO PARA LA PREVENCIÓN Y
TRATAMIENTO DE LA HIPERLIPIDEMIA**

Campo de la Invención

5

La presente invención se relaciona con el campo de agentes terapéuticos útiles para bajar el colesterol o mejorar la proporción de HLD:LDL (particularmente bajar las lipoproteínas de baja densidad y/o incrementar las lipoproteínas de alta densidad) y/o ésteres de colesterilo, triglicéridos, fosfolípidos y ácidos grasos en un mamífero, tal como un humano. Más particularmente, la invención se relaciona con terapias de combinación, usos y composiciones farmacéuticas que tienen mayores beneficios terapéuticos que las monoterapias utilizando las mismas sustancias terapéuticas.

Antecedentes de la Invención

20 Es bien conocido que las condiciones hiperlipidémicas asociadas con concentraciones elevadas del colesterol total y lipoproteína de baja densidad (LDL) colesterol son factores de mayor riesgo para las enfermedades cardiovasculares tales como la aterosclerosis. Numerosos estudios han demostrado que
25 una concentración baja en plasma de lipoproteína de alta densidad (HDL) colesterol (el buen colesterol) es un factor de riesgo poderoso para el desarrollo de la aterosclerosis (Barter y Rye, Atherosclerosis, 121, 1-12 (1996)). El HDL es

una de las clases principales de lipoproteínas que funciona en el transporte de lípidos por la sangre. Los lípidos principales encontrados asociados con el HDL incluyen el colesterol, el éster de colesterilo, los triglicéridos, fosfolípidos y ácidos grasos. Las otras clases de lipoproteínas encontradas en la sangre son lipoproteínas de baja densidad (LDL). La lipoproteína de densidad intermedia (IDL), y la lipoproteína de muy baja densidad (VLDL). Ya que bajos niveles del colesterol HDL incrementan el riesgo de la aterosclerosis, los métodos para elevar el colesterol HDL en el plasma serían beneficiosos terapéuticamente para el tratamiento de enfermedades cardiovasculares tales como la aterosclerosis. Las enfermedades cardiovasculares incluyen, pero no se limitan a, enfermedad coronaria del corazón, enfermedad vascular periférica e infartos.

Un modelo para dirigir la hiperlipidemia ha sido el uso de poliglucosamina, una sustancia derivada de la concha de los crustáceos. La poliglucosamina es un derivado de chitina altamente desacetilado y de bajo peso molecular. Como se describió en la Patente Canadiense No. 2, 085, 292, el tratamiento enzimático de chitosan con una enzima de hidrolasa resulta en derivados de chitosan que tienen un peso molecular disminuido, viscosidad disminuida y una solubilidad incrementada del chitosan en agua.

En su mecanismo de acción, la poliglucosamina contiene grupos amina libres que se sujetan ellos mismos a los lípidos tales

como el colesterol mediante enlaces iónicos mientras que en el tracto intestinal, forman un complejo indisociable que es excretado eventualmente. La poliglucosamina por lo tanto impide que los lípidos tales como del colesterol ingresen para siempre en la corriente sanguínea y se agreguen al contenido del colesterol total. Comúnmente es utilizado en dosis de 400 a 800 mg/tres veces al día, con comidas y según se indicó hacia la obtención de un perfil de lípido saludable y más particularmente un perfil de colesterol saludable. La poliglucosamina es bien tolerada por los pacientes. Efectos colaterales reportados en los niveles de dosificación indicados anteriormente han sido suaves o ninguno. (Veneroni G. Veneroni F. Contos S et al. Effect of a new chitosan dietary integrator and hypocaloric diet on hyperlipidemia and overweight in obese patients. Acta toxicol the 1996 17 (1): 53-60).

La poliglucosamina se encuentra comercializada actualmente por Magistral Biotech bajo los nombres comerciales Libracol® (HEP-30) en cápsulas de gelatina de 800 mg.

Otra terapia conocida es el uso del fibrato para bajar el colesterol en la sangre. Los fibratos son drogas que bajan el colesterol que son efectivas principalmente en bajar los triglicéridos y, a un menor grado, en incrementar niveles de colesterol HDL. Varias drogas de fibrato están disponibles comercialmente tales como Gemfiprozil disponible bajo el nombre comercial LOPID. LOPID es el fibrato más ampliamente

utilizado en los Estados Unidos y puede ser muy efectivo para
pacientes con niveles de triglicéridos. Sin embargo, este no
es muy efectivo para bajar el colesterol LDL. Como resultado,
es usado menos frecuente que otras drogas y pacientes con
5 enfermedades del corazón para quienes bajar el colesterol LDL
es el objetivo del tratamiento principal. Se debe notar que
Gemfibrozil como monoterapia no es recomendado por la
administración de alimentos y drogas de los Estados Unidos
para pacientes con enfermedad cardíaca.

10

De otro lado, los fibratos son generalmente bien tolerados
por la mayoría de los pacientes. Quejas gastrointestinales
son los efectos colaterales más comunes y los fibratos
parecen incrementar la probabilidad de desarrollar cálculos
15 biliares por colesterol. El fibrato puede incrementar las
medicaciones efectivas que adelgazan la sangre. Los fibratos
pueden ser dados usualmente en dos dosis diarias, 30 minutos
antes en la mañana, y en la noche antes de las comidas. Las
reducciones en los triglicéridos generalmente están en el
20 rango de 20% a 50% con un incremento en el colesterol HDL del
10 al 15%. Otras drogas de fibrato incluyen Estiprofibrato,
Belzafibrato; y Finofibrato.

Otro modelo terapéutico bien conocido para tratar o impedir
25 las condiciones hiperlipidémicas es el uso de inhibidores de
HMG-CoA reductasa (incluyendo las clases de terapéuticos
comúnmente llamados "estatinas"). Las estatinas se conocen
porque reducen los niveles en el suero sanguíneo del

colesterol LDL mediante la inhibición competitiva de la etapa biosintética. Diversas estatinas se han desarrollado y comercializado en todo el mundo. El calcio de atorvastatina vendido en Norte América bajo la marca Lipitor® es un

5 inhibidor potente de la reductasa. Sin embargo, anuncios de efectos colaterales por el uso de las estatinas incluye la disfunción de ligado, miopatía muscular esquelética, rabdomiolisis y falla renal aguda. Algunos de estos efectos son exacerbados cuando las estatinas se toman en grandes

10 dosis. Por ejemplo, un paciente tratado con 10 mg por día de Lipitor puede notar efectos colaterales suaves mientras que los efectos colaterales se pueden incrementar grandemente simplemente elevando la dosis diaria a 20 mg por día. De hecho, en Agosto 8 de 2001, el fabricante de cerivastina

15 voluntariamente retiró la medicina del mercado por las numerosas muertes asociadas con su uso. Las muertes fueron causadas por complicaciones de rompimiento severo de los músculos.

20 Un número de terapias de combinación para el tratamiento de la enfermedad cardiovascular, que incluye la estatina como un de los componentes activos se conoce. Más precisamente, la terapia de combinación de estatina y fibrato es bien conocida. Sin embargo, estudios recientes han mostrado que el

25 riesgo de desarrollar rabdomiolisis incrementa 1400 veces cuando las estatinas son combinadas con los fibratos. Este riesgo es aún más prevalente en pacientes con diabetes quienes combinan estos dos tipos de medicamentos, produciendo tanto

como una persona entre 500 afectadas con rabdomiolisis
(<http://www.wnbc.com/drmaxgomez/393553/details.html>).

Otro ejemplo de una terapia de combinación de fluvastatina y
5 niceritrol se describe por J. Sasaki et al. (int. J. Clin.
Pharmacol. Ther., Julio: 33(7), 420-6 (1995)). Aquellos
investigadores concluyen que la combinación de fluvastatina
con niceritrol, "una dosis de 750 mg/día no parece aumentar o
atenuar efectos benéficos de la fluvastatina."

10

L. Cashin-Hemphill et al. (J. Am. Med. Assoc., 264 (23),
3013-17 (1990)) describe los efectos beneficiosos de una
terapia de combinación de colestipol y niacina a la
aterosclerosis coronaria.

15

Una terapia de combinación de acipimox y simvastatina muestra
efectos benéficos en pacientes que tienen altos niveles de
triglicéridos (N. Hoogerbrugge et al., J. internal Med., 241,
151-55 (1997)).

20

En un estudio sobre la reducción de biomarcadores
inflamatorios mediante la estatina, el fibrato y la terapia
de combinación entre pacientes diabéticos con dislipidemia
mezclada (G Am Coll Cardiol. 2006 Jul. 18; 48 (2): 396-401),
25 se ha reportado que los efectos anti inflamatorios en terapia
de combinación no fueron más efectivos que la forma de
monoterapia.

Así, existe una necesidad para buscar estrategias para bajar el colesterol alternativas que sean seguros y no presente efectos colaterales severos suficientes para crear problemas de salud adicionales tales como la rabdomiolisis. Más particularmente, existe una necesidad para suministrar nuevos modelos terapéuticos que tengan las ventajas proporcionadas por las terapias de combinación (modo complementario de acción) mientras que también sean seguras y eficientes. La presente invención suministra tales nuevos modelos terapéuticos en la forma de nuevas combinaciones de agentes reductores del colesterol que son compatibles y así son seguros de utilizar mientras por lo menos son efectivos como las monoterapias correspondientes para cada uno de los agentes reductores del colesterol correspondientes presentes en la combinación

Resumen de la Invención

Una modalidad de la presente invención suministra una composición farmacéutica que comprende: a) una cantidad farmacéuticamente efectiva de fibrato; b) una cantidad farmacéuticamente efectiva de poliglucosamina y opcionalmente c) un portador farmacéuticamente aceptable.

Una modalidad de la presente invención también suministra el uso de la composición farmacéutica anteriormente definida para incrementar el nivel de HDL en la sangre de un mamífero.

Una modalidad adicional de la presente invención suministró el uso de la composición farmacéutica anteriormente definida para bajar el nivel de lipoproteína de baja densidad en la sangre de un mamífero.

5

Una modalidad adicional de la presente invención suministra un método para bajar la concentración de lipoproteína de baja densidad en la sangre de un mamífero y/o mejorar la proporción de HLD:LDL en tal mamífero mediante incrementar el
10 nivel de las lipoproteínas de alta densidad; el método comprende la etapa de administrar una composición farmacéutica de la invención o a) una primera cantidad de un fibrato y b) una segunda cantidad de poliglucosamina; en donde la primera y segunda cantidades juntas comprenden una
15 cantidad terapéuticamente efectiva.

Otra modalidad suministra un método para la profilaxis o tratamiento de la hiperlipidemia o afección asociada a hiperlipidemia que comprende administrar a un paciente: a)
20 una primera cantidad de un fibrato y b) una segunda cantidad de poliglucosamina; en donde la primera y segunda cantidades juntas comprenden una cantidad terapéuticamente efectiva.

En una modalidad adicional suministra un kit para la
25 profilaxis o tratamiento de la hiperlipidemia o afección asociada a la hiperlipidemia en un mamífero que comprende una pluralidad de dosis diarias de formas de dosificación de un fibrato, una pluralidad de dosis diarias de formas de

purificación de poliglucosamina juntas, e instrucciones escritas para el tratamiento o régimen.

La presente invención tiene una ventaja de suministrar una
5 terapia alternativa para bajar el colesterol en la sangre mediante combinar inesperadamente agentes activos en la reducción del colesterol que son compatibles en naturaleza. Tales combinaciones permiten el uso de una cantidad reducida de cada uno de los agentes activos reductores del colesterol,
10 reduciendo así sus efectos colaterales.

Descripción Detallada de la Invención

La presente invención suministra terapias de combinación que
15 tienen un mecanismo dual reductor del colesterol que permite reducir el colesterol de manera efectiva con efectos colaterales reducidos en comparación con las monoterapias correspondiente. Cuando nos referimos a mecanismo dual reductor de colesterol, quiere decir, una reducción del
20 colesterol total en la sangre mediante dos modos fisiológicos de acción.

La presente invención mejora los esfuerzos para impedir y/o tratar la hiperlipidemia, de modo que mediante reducir el
25 colesterol en el suero, mediante suministrar un modelo de terapia de combinación y una composición farmacéutica novedosa que suministra beneficios terapéuticos tales como seguridad y efectos colaterales reducidos no disponible

mediante otras terapias mono o múltiples conocidas para la hiperlipidemia. La presente invención suministra los beneficios proporcionados por el fibrato en una terapia de combinación que de otra manera sería contraindicado si se
5 utilizara en combinación con otros agentes reductores del colesterol conocidos tales como la estatina. La combinación poliglucosamina/fibrato de la presente invención permite que un paciente se beneficie de los efectos complementarios
10 duales reductores del colesterol de cada uno de estos agentes sin efectos adversos causados por la incompatibilidad de los dos agentes. La invención por lo tanto descansa en la nueva combinación de poliglucosamina y fibrato como una terapia segura y eficiente para reducir el colesterol en la sangre.

15 La presente invención suministra una terapia de combinación para reducir el colesterol en la sangre que comprende una combinación de por lo menos un fibrato y una poliglucosamina. Preferiblemente, el fibrato se selecciona del grupo que
20 consiste de ciprofibrato, gemfibrozil; benza fibrato; y fenofibrato. También preferiblemente, la poliglucosamina es una sal de chitosan que tiene un peso molecular menor que 650 kDa y tiene un grado de desacetilación de alrededor de 70% a 100 %.

25 La presente invención también suministra un método para reducir el colesterol en la sangre y/o incrementar la proporción HDL/LDL mediante incrementar el nivel de HDL mediante administrar a un mamífero la composición

farmacéutica de la presente invención o mediante administrar una composición que comprende una cantidad efectiva de fibrato y poliglucosamina.

- 5 La presente invención también suministra un método para la profilaxis o tratamiento de la hiperlipidemia o afección asociada a la hiperlipidemia que comprenden administrar a un paciente la composición farmacéutica de la presente invención o una composición que comprende una cantidad efectiva de
10 por lo menos un fibrato o poliglucosamina.

- La presente invención suministra adicionalmente una forma de dosificación oral de una composición farmacéutica que comprende una combinación de poliglucosamina y fibrato en
15 donde la forma de dosificación suministra a un mamífero que necesita el tratamiento mediante la poliglucosamina y el fibrato, una dosis terapéuticamente efectiva de poliglucosamina y una cantidad terapéuticamente efectiva de fibrato en la sangre de dicho mamífero.

20

- La presente invención también suministra un kit para la profilaxis o tratamiento de la hiperlipidemia en un mamífero. El kit comprende una pluralidad de dosis diarias de formas de dosificación de un fibrato y de una poliglucosamina juntas
25 con unas instrucciones del régimen o del tratamiento.

Las combinaciones de la presente invención tendrán un número de ventajas por ejemplo, mediante el ajuste de la

dosificación y el monitoreo médico, las dosificaciones individuales de los compuestos terapéuticos utilizados en las combinaciones de la presente invención serán menores que las dosificaciones típicas de los compuestos terapéuticos cuando se utilizan en monoterapias. La dosificación más baja suministra ventajas incluyendo la reducción de los efectos colaterales de los compuestos terapéuticos individuales cuando de compara con la monoterapia. Adicionalmente, los efectos colaterales menores de la terapia de combinación comparada con las monoterapias llevarán a una mayor complacencia del paciente con los regímenes de la terapia.

Otra ventaja suministrada por la terapia de combinación de la presente invención es que esta suministra un mecanismo dual reductor del colesterol que consiste de efectos complementarios o modos complementarios de acción para reducir el colesterol en la sangre. Por ejemplo, el fibrato puede controlar los niveles de colesterol en el suero sanguíneo mediante disminuir los triglicéridos del suero mediante la producción hepática reducida y la clarificación de triglicéridos incrementada mediante los tejidos periféricos y el incremento del HDL. En contraste, la poliglucosamina puede bloquear la migración del colesterol y/o otros lípidos tales como los ésteres de colesterilo y triglicéridos desde el tracto intestinal a la corriente sanguínea, y la reabsorción de los ácidos biliares del tracto intestinal en la corriente sanguínea.

Una ventaja adicional de la terapia de combinación suministrada por la presente invención es que es segura de utilizar debido a la muy baja incidencia de efectos colaterales o de eventos adversos causados por la combinación de la misma. En el presente caso, el fibrato es combinado con una poliglucosamina que es un biopolímero de ocurrencia natural que también es conocido por ser útil en bajar el colesterol sanguíneo. Como se indicó previamente, la poliglucosamina actualmente es comercializada por magistral como un suplemento dietético bajo el nombre Libracol® (HEP 30) en cápsulas de gelatina de 800 ml.

Definiciones

Como se utiliza aquí, el término "fibrato" se refiere a una clase de ácido anfipáticos carboxílicos. Estos se utilizan para un rango de trastornos metabólicos principalmente la hipercolesterolemia (alto colesterol), hiperlipidemia y por lo tanto son agentes hiperlipidémicos.

20

Como se utiliza aquí, "chitina" se refiere a un polímero formado principalmente de unidades repetitivas de β (1-4) 2-acetamido-2-deoxi-D-glucosa (o N-acetilglucosamina). No cada unidad de las chitina de ocurrencia natural es acetilada, con cerca del 16% de desacetilación.

25

Como se utilizó aquí, "chitosan" se refiere a chitina que ha sido parcialmente o completamente desacetilada. El chitosan

es un polisacárido formado principalmente de unidades repetitivas de β (1-4) 2-amino-2-deoxi-D-glucosa (o D-glucosamina). La desacetilación adicional de la chitina se puede lograr mediante el procesamiento de la chitina. Los
5 valores de desacetilación pueden variar con las fuentes de chitina y con los métodos de procesamiento.

Como se utilizó aquí, el término "poliglucosamina" o el término "chitodextrina", se refiere a un polímero de chitosan
10 que tiene un peso molecular menor que cerca de 650 kDa, preferiblemente cerca de 2 a 500 kDa, más preferiblemente cerca de 15 a 200 kDa, todavía más preferiblemente cerca de 20 a 100 kDa, y aún todavía más preferiblemente alrededor de 25 a 60 kDa, e idealmente alrededor de 30 a 50 kDa. En una
15 modalidad. El peso molecular de la poliglucosamina es de alrededor de 30 kDa y en otra modalidad, el peso molecular es alrededor de 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, o 50 kDa. La poliglucosamina se puede obtener mediante romper una cadena molecular más
20 pesada de chitosan. Preferiblemente, la poliglucosamina es altamente desacetilada, tal como sobre cerca de 80%, y más preferiblemente por encima de 89%. La poliglucosamina se entiende aquí que también abarca una sal de chitosan formada de cualquier molécula de chitosan asociado con un anión
25 cargado negativamente. Una serie de aniones se ha utilizado para este propósito. Por ejemplo, aniones derivados de ácidos inorgánicos tales como ácido sulfúrico (sulfato), ácido fosfórico (fosfato), ácido clorhídrico (cloruro) y ácidos

orgánicos tales como el ácido málico (malato), ácido tartárico (tartrato), ácido cítrico (citrato), ácido succínico (succinato) y ácido láctico (lactato), chitina, chitosan y sus derivados.

5

Como se utilizó aquí el término "terapia de combinación" se refiere a la administración de dos o más agentes terapéuticos para tratar una afección hiperlipidémica, por ejemplo la aterosclerosis y la hipercolesterolemia. Tal administración
10 abarca la co-administración de estos agentes terapéuticos de una manera sustancialmente simultánea, tal como en una cápsula única que tiene una proporción fija de los ingredientes activos o en formas de dosificación múltiples o separadas para cada tipo de agente terapéutico de una manera
15 secuencial o escalonado. En cualquier caso, el régimen de tratamiento suministrará efectos benéficos de la combinación de la droga al tratar la afección hiperlipidémica.

Como se utiliza aquí "nutracéuticos" se entiende que abarca
20 cualquier alimento ordinario que tiene componentes o ingredientes agregados para dar un beneficio médico o fisiológico específico además de un efecto puramente nutricional. También se entiende que incluye alimentos funcionales, suplementos dietéticos y productos vendidos en
25 mostrador sin una prescripción.

Como se utilizó aquí, "alimentos funcionales", se entiende que abarca cualquier alimento consumido como parte de una

dieta usual que es similar en apariencia a, o puede ser, un alimento convencional, y está demostrado que tiene beneficios fisiológicos y/o reduce el riesgo de enfermedades crónicas más allá de las funciones nutricionales básicas.

5

La frase "terapéuticamente efectivo" tiene el propósito de calificar la cantidad de ingrediente activo en la terapia de combinación que logrará el objetivo de reducir o eliminar la afección hiperlipidémica.

10

La frase "compuesto terapéutico" se refiere a un compuesto útil en la profilaxis o tratamiento de una afección hiperlipidémica, tal como, pero sin limitarse a, aterosclerosis, hipercolesterolemia, enfermedad coronaria del corazón, y enfermedad cardiovascular.

15

La frase "Farmacéuticamente efectivo" tiene el propósito de calificar la cantidad del ingrediente que logrará el objetivo propuesto para la composición farmacéutica.

20

La frase "mecanismo dual reductor de colesterol" significa la reducción del colesterol total en la sangre mediante dos modos de acción distintos fisiológicos.

25 **Poliglucosamina**

Poliglucosamina se refiere a un polímero de chitosan que tiene un peso molecular de menos de cerca de 650 kDa,

preferiblemente cerca de 2 a 500 kDa, más preferiblemente aproximadamente 15 a 200 kDa, todavía más preferiblemente aproximadamente de 20 a 100 kDa, y aún más preferiblemente aproximadamente de 25 a 60 kDa, e idealmente aproximadamente de 30 a 50 kDa.

El quitosán es un biopolímero de ocurrencia natural que también se puede obtener mediante desacetilación parcial o completa de la quitina que es el componente principal del exoesqueleto de los peces con concha e insectos. El quitosán es por lo tanto un polímero lineal compuesto de monómeros de N-acetil-2-amino- β -D-glucosa y 2-amino- β -D-glucosa. La presencia de los grupos amino principales de la 2-amino- β -D-glucosa (D-glucosamina) en unidades le confiere al quitosán un carácter policatiónico (cargado positivamente) que es neutralizado mediante los aniones cargados negativamente adjuntos. Una serie de aniones se han utilizado para este propósito. Por ejemplo, aniones derivados de ácidos inorgánicos tales como ácido sulfúrico (sulfato), ácido fosfórico (fosfato), ácido clorhídrico (cloruro) y una mezcla de estos y ácidos orgánicos tales como el ácido málico (malato), ácido tartárico (tartrato), ácido acético (acetato), ácido fórmico (formato), ácido glicólico (glicolato), ácido oxálico, ácido succínico, ácido ascórbico, ácido maleico, ácido acrílico, ácido glucónico, ácido glutámico, ácido propiónico y una mezcla de estos se ha reportado como sales de quitosán.

Aunque existen muchos métodos de extracción de la chitina de las conchas de los crustáceos, los principios de la extracción de la chitina son relativamente simples. En un cierto tratamiento, las proteínas se remueven en una solución diluida de hidróxido de sodio (tal como aproximadamente de 1% a 10%) a alta temperatura (tal como aproximadamente 85° C a 100° C). Las conchas son entonces desmineralizadas para remover el carbonato de calcio. Esto se puede hacer mediante tratarlas en una solución diluida de ácido clorhídrico (1% a 10%) a temperatura ambiente. Dependiendo de la severidad de estos tratamientos, tal como temperatura, duración, concentración de los químicos, concentración y tamaño de las conchas molidas, las características físico químicas de la chitina extraída pueden variar. Por ejemplo, tres características de la chitina tal como el grado de polimerización, la acetilación y la pureza se pueden afectar. La concha también contiene lípidos y pigmentos. Por lo tanto, una etapa de descolonización se requiere algunas veces para obtener una chitina blanca. Esto se puede hacer mediante sumergir en disolventes orgánicos o en una solución muy diluida de hipoclorito de sodio. Nuevamente, estos tratamientos pueden influenciar las características de la molécula de chitina.

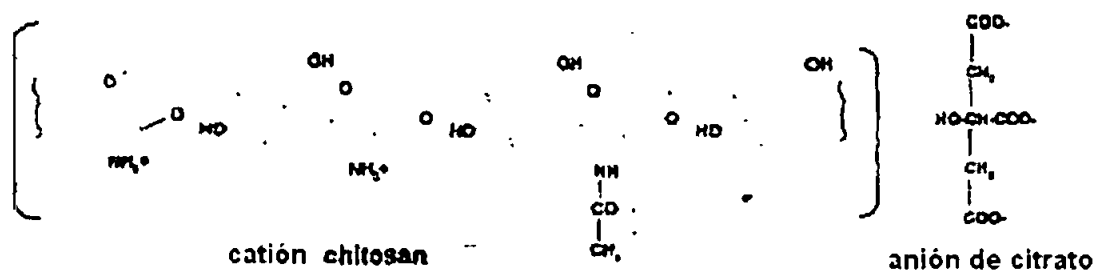
25 La chitina se puede desacetilar parcialmente o totalmente. Tal polímero desacetilado se llama chitosan. Los compuestos de chitosan en un rango de hasta y excediendo 1×10^6 de peso molecular son derivados comercialmente de la chitina. En la

naturaleza, el chitosan está presente en las paredes celulares de los cigomicetos, un grupo de hongos fitopatogénicos. Debido a su contenido significativo de grupos amino libre, el chitosan tiene un carácter
5 marcadamente catiónico y tiene una carga positiva en la mayoría de los PH. La patente Canadiense 2,085,292 divulga la hidrólisis del chitosan, la divulgación de la cual se incorpora aquí como referencia.

10 La poliglucosamina se puede producir mediante el proceso descrito en la patente Canadiense 2, 085, 292, y recuperada de la solución utilizando el proceso descrito en la WO 2005/066213-A1 en donde el chitosan es salado con una sal para sal cal como pero sin limitarse a sulfatos, fosfatos,
15 citratos, nitratos, malatos, tartratos, succinatos, propionatos, lactatos, e hidrogenfosfatos. Más preferiblemente, estas sales para salar se pueden seleccionar del grupo que consiste de: sulfato de amonio o de sodio; fosfatos de sodio o de potasio; citrato de sodio o potasio;
20 tartrato de sodio; malato de sodio; nitrato de sodio; lactato de sodio; malonato de sodio; succinato de sodio; acetato de sodio; propionato de sodio. Así, la presente invención incluye cualquier derivado de chitosan obtenido por cualquiera de las sales anteriormente mencionadas.

25

Como un ejemplo, la sal de citrato de chitosan se puede ilustrar como sigue:



Poliglucosamina.

- 5 En un mecanismo de acción, la poliglucosamina, en particular el chitosan, puede contener grupos amina libres que se pueden sujetar ellos mismos a lípidos, tales como el colesterol, mediante enlaces iónicos mientras que en el tracto intestinal, formando un complejo indisociable que es
- 10 eventualmente excretado. La poliglucosamina por lo tanto puede impedir que los lípidos, tales como el colesterol entren alguna vez a la corriente sanguínea y se agreguen al contenido total de colesterol. También, en reacción, el
- 15 hígado elimina la mayor parte del colesterol mediante utilizar ácidos biliares. Por lo tanto, existe eliminación tanto del colesterol en la comida y aquel de los ácidos biliares ricos en colesterol.

Peso molecular

20

La poliglucosamina tiene muchas aplicaciones potenciales dependiendo de su peso molecular. Un peso molecular en promedio alto de poliglucosamina es de alrededor de 650 kDa. Algunas aplicaciones son típicas de poliglucosamina de medio

o bajo peso molecular, que varía típicamente entre 2 a 500 KDa. Estas aplicaciones incluyen su uso como un agente anti-hongos; un recubrimiento para semillas para mejorar la producción de las cosechas; un elixir de reacciones naturales antipatogénicas en plantas; un agente hipocolesterolémico en animales; un acelerador de las bacterias de ácido láctico en las cosechas, y un agente retenedor de humedad para lociones, tónicos para el cabello y otros cosméticos. El peso molecular de la poliglucosamina es un rasgo que es particular a cierta aplicación. El peso molecular de la chitina nativa se ha reportado que es tan alto como varios millones de Daltons. Sin embargo, el tratamiento químico tiende a bajar el peso molecular de la poliglucosamina, para ubicarse entre 100 kDa a 1500 kDa. Un tratamiento adicional de la poliglucosamina puede disminuir o bajar más el peso molecular. El peso molecular bajo se puede producir mediante diferentes maneras incluyendo métodos enzimáticos o químicos. Cuando la cadena se vuelve más corta, la poliglucosamina se puede disolver directamente en agua sin la necesidad de un ácido. Esto es particularmente útil para aplicaciones específicas, tales como en cosméticos o en medicina. El peso molecular de la poliglucosamina se puede medir mediante métodos analíticos, tales como cromatografía por permeación de gel, difracción de luz, o discometría. Debido a la simplicidad, la discometría es el método más comúnmente utilizado.

En una modalidad, el peso molecular de poliglucosamina es de aproximadamente 30 kDa y en otra modalidad, el peso molecular es de aproximadamente 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, o 50 kDa. La poliglucosamina se puede obtener mediante romper una cadena molecular más pesada de chitosan.

Desacetilación

La chitina se puede desacetilar parcial o totalmente. La chitina de ocurrencia natural es acetilada, con cerca de 16% de desacetilación. El chitosan se refiere a chitina que ha sido parcial o completamente desacetilada. El chitosan es un polisacárido formado principalmente de unidades repetitivas de β (1-4) 2-amino-2-deoxi-D-glucosa (o D-glucosamina). La desacetilación adicional de la chitina se puede lograr mediante el procesamiento de la chitina. Los valores de desacetilación pueden variar con las fuentes de chitina y con los métodos de procesamiento.

20

Ya que el chitosan está hecho mediante la desacetilación de la chitina, el término grado de desacetilación (DAC) se puede utilizar para caracterizar el chitosan. Este valor da la proporción de unidades monoméricas de las cuales los grupos acetílicos que se han removido indican la proporción de grupos amino libres (reactivos después de la disolución en ácido débil) sobre el polímero. El DAC podría variar entre alrededor de 70% hasta aproximadamente 100%, dependiendo del

método de fabricación utilizado. Este parámetro indica la carga catiónica de la molécula después de la disolución en un ácido débil. Existen muchos métodos de mediciones de DAC, tal como espectroscopia de UV o de infrarrojos, titulación por ácido-base, resonancia magnética nuclear, absorción de tinturas, y similares. Ya que no existen métodos estándares o no oficiales, los números tienden a ser diferentes para los múltiples métodos. En un producto de alto valor, el RMN puede dar un número DAC preciso. Sin embargo, la titulación o la absorción de tintas pueden servir como un método rápido y conveniente y proporcionar resultados similares a la RMN.

La desacetilación de la chitina hacia el chitosan se puede obtener mediante varios métodos. El método más utilizado es aquel del tratamiento alcalino (Horowitz S. T. et al., 1957). Con este método, aproximadamente un 80% de desacetilación se puede lograr sin disminuir significativamente el peso molecular. Una desacetilación más intensa no se puede obtener por este método sin una disminución simultánea y no controlada del grado de polimerización. Un método más prometedor es la desacetilación mediante un tratamiento termo-mecano-químico (Pelletier et al., 1990). Este método permite un control más cuidadoso de las varias características del producto final (grado promedio de polimerización y de desacetilación). Finalmente, un tercer método (Domard y Rinaudo, 1983) permite obtener un producto totalmente desacetilado.

En un cierto protocolo de desacetilación, cuando la chitina se calienta en una solución básica, tal como una solución fuerte de hidróxido de sodio (tal como aproximadamente 40%) a alta temperatura (tal como aproximadamente 90° C a 120° C), el chitosan se forma mediante la desacetilación. Este tratamiento puede remover los grupos acetílicos sobre los radicales amina a un producto (chitosan) que podría ser disuelto. Se dice que por lo menos 65% de los grupos acetílicos se deberían remover en cada chitina monomérica para obtener la habilidad de ser colocada en solución. El grado de desacetilación variará de acuerdo con las condiciones del tratamiento, tal como la duración, la temperatura y la concentración de la solución básica.

En modalidades preferidas. La poliglucosamina tiene una desacetilación mayor que aproximadamente 80%. Preferiblemente, la poliglucosamina tiene una desacetilación mayor de aproximadamente 89%. Más preferiblemente, la poliglucosamina tiene una desacetilación mayor que cerca de 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, o 100%. En una poliglucosamina que ha sido desacetilada alrededor del 100%, la ventaja es las formas de poliglucosamina de una composición relativamente homogénea.

De acuerdo con la presente invención, la poliglucosamina tiene un peso molecular de alrededor de 30 kDa y es desacetilada en por lo menos un 80%. En una modalidad preferida, la poliglucosamina tiene un peso molecular de

alrededor de 30 kDa y es desacetilada por lo menos en un 93% y es vendida bajo la marca Libracol® en Canadá

Fibrato

5

Los fibratos con una clase de ácidos carboxílicos anfipáticos. Sus acciones principales son las de disminuir los triglicéridos en el suero e incrementar el HDL. Ellos actúan mediante la activación de los receptores activados por el proliferador peroxisoma (PPAR) α que están involucrados en la regulación de un número de genes involucrados en el metabolismo de los lípidos. Los fibratos también son efectivos para la reducción de la concentración circulante del LDL bajamente tenso. En una modalidad de la presente invención, el fibrato se selecciona del grupo que consiste de ciprofibrato, gemfibrozil; benza fibrato; y fenofibrato. Preferiblemente, el fenofibrato se utiliza en la terapia de combinación de la presente invención.

20 Sinergismo

La sinergia o el sinergismo, más frecuentemente se refieren al fenómeno de dos o más influencias discretas o agentes que actúan en común para crear un efecto que es mayor que la suma de los efectos de cada uno creados independientemente. La advertencia de efectos colaterales del uso del fibrato incluye el deterioro renal, el deterioro hepático severo, la hipoalbuminemia, cirrosis biliar primaria, enfermedad de

cálculos en la vejiga, y síndrome nefrótico. Algunos de estos efectos se notan cuando el fibrato se toma en dosis regulares de por lo menos aproximadamente 1200 mg por día.

- 5 De acuerdo a lo anterior, una ventaja de utilizar el sinergismo de la droga es la habilidad de utilizar una cantidad reducida de fibrato para el mismo resultado que en la monoterapia de fibrato, así, resultante en efectos colaterales menores.

10

Prevención y tratamiento de condiciones

- Las modalidades preferidas se pueden utilizar para impedir, aliviar de o mejorar una afección de enfermedad que tiene y
- 15 la hiperlipidemia como un elemento de una enfermedad, tal como la aterosclerosis o la enfermedad coronaria del corazón, o para proteger contra o tratar adicionalmente el alto colesterol en el plasma o en la sangre con los compuestos y/o composiciones de las modalidades preferidas. La
- 20 hiperlipidemia es una elevación de los lípidos (grasas) en la corriente sanguínea. Estos lípidos incluyen el colesterol, los ésteres de colesterol (compuestos), fosfolípidos, triglicéridos, y ácidos grasos. Estos lípidos se transportan en la sangre como parte de moléculas grandes llamadas
- 25 lipoproteínas.

Los eventos adversos de la hiperlipidemia incluyen aterosclerosis y enfermedad coronaria del corazón. La

aterosclerosis es una enfermedad caracterizada por la deposición de lípidos, incluyendo colesterol, en la pared de los vasos arteriales, resultando en un estrechamiento del paso de los vasos y en un endurecimiento del sistema vascular. La causa principal de la enfermedad coronaria del corazón (CHD) es la aterosclerosis. El CHD ocurre cuando las arterias que suministran la sangre al músculo del corazón (arterias coronarias) se endurecen y se estrechan. Como resultado del CHD, pueden venir la angina y ataque al corazón. Con el tiempo, el CHD puede debilitar su músculo del corazón y contribuir a una falla cardíaca o arritmias.

La hipercolesterolemia está también vinculada a la enfermedad cardiovascular. La enfermedad cardiovascular se refiere a enfermedades del corazón y enfermedades del sistema de vasos sanguíneos (arterias, capilares, venas) dentro del cuerpo completo de la persona, tal como el cerebro, las piernas, y los pulmones. Las enfermedades cardiovasculares incluyen, pero no se limitan a, enfermedad coronaria del corazón, enfermedad vascular periférica, e infarto.

De acuerdo a lo anterior, una modalidad de la presente invención se relaciona con el uso de la terapia de combinación de poliglucosamina y fibrato para disminuir el colesterol en la sangre en un mamífero. Preferiblemente, el mamífero es un humano.

De acuerdo a lo anterior, otra modalidad de la presente invención se relaciona con el uso de la terapia de combinación de la poliglucosamina y el fibrato en la prevención o tratamiento de la hiperlipidemia y condiciones
5 asociadas con la hiperlipidemia tal como la hipercolesterolemia, aterosclerosis, enfermedad coronaria del corazón, y enfermedad cardiovascular.

Se debería entender que la terapia de combinación de
10 poliglucosamina y fibrato como se mencionó anteriormente puede estar en la forma de una composición farmacéutica de acuerdo con la presente invención o de cualquier otra composición que comprenda una combinación de poliglucosamina y fibrato. En el caso de tal composición, la naturaleza y
15 cantidad de la poliglucosamina y el fibrato puede ser similares a aquellas especificadas en la composición farmacéutica de la presente invención. Una persona versada en la técnica podría fácilmente determinar la cantidad exacta con base en la información suministrada en la presente
20 solicitud.

Composiciones farmacéuticas

Los compuestos útiles en las modalidades preferidas se pueden
25 presentar con un vehículo aceptable en la forma de una composición farmacéutica. El vehículo es aceptable en el sentido de ser compatible con los otros ingredientes de la composición y que no sea dañino al receptor. El portador

puede ser un sólido o un líquido, o ambos, y se formula preferiblemente con el compuesto como una composición de dosis unitaria, por ejemplo, una cápsula o tableta, que puede contener entre aproximadamente 0.05% a aproximadamente 95% en peso del compuesto activo. Ejemplos de portadores adecuados, diluyentes, excipientes, incluyen, pero no se limitan a, lactosa, dextrosa, sacarosa, sorbitol, manitol, almidones, goma de acacia, alginatos, tragacanto, gelatina y silicato de calcio, celulosa, carbonato de magnesio, o un fosfolípido con el cual el polímero pueda formar una miscela. Otras sustancias farmacológicamente activas también pueden estar presentes, incluyendo otros compuestos de las modalidades preferidas. Por ejemplo, más de un fibrato se puede utilizar junto. Las composiciones farmacéuticas de las modalidades preferidas se pueden preparar mediante cualquiera de las técnicas de farmacia bien conocidas, que comprende mezclar los componentes.

Al practicar los métodos de las modalidades preferidas, la administración de fibrato, en terapia de combinación, se puede llevar a cabo por vía oral.

Para la administración oral, los compuestos utilizados en la terapia de combinación pueden estar en la forma de, por ejemplo, sin limitarse a, una tableta, cápsula, suspensión, polvos (por ejemplo para esparcir sobre la comida) o líquidos. Otras modalidades incluyen cápsulas de liberación sostenida, tabletas entéricas recubiertas, cápsulas de

gelatina suave, y otras tecnologías de liberación sostenida. Las cápsulas, tabletas, líquidos o polvos, y similares se pueden preparar mediante métodos convencionales bien conocidos en la técnica. Los compuestos están preferiblemente
5 hechos en la forma de una unidad de dosificación que contiene una cantidad especificada del compuesto. Ejemplos de unidades de dosificación son las tabletas o cápsulas.

Las composiciones farmacéuticas para uso en los métodos de
10 tratamiento de las modalidades preferidas se pueden administrar en forma oral para compuestos de la composición, o mediante forma parenteral, tal como administración intravenosa para el fibrato y administración oral para la poliglucosamina. Por conveniencia, la administración oral de
15 ambas sustancias terapéuticas es la preferida. La dosis para administración oral puede ser con un régimen llamado dosis diaria única, o para una dosis única cada tercer día o para múltiples dosis espaciadas o separadas durante el día.

20 Nutraceuticos

Los compuestos útiles en la presente invención se pueden incorporar en un alimento funcional o nutraceutico. Estos compuestos pueden estar presentes en la forma de agentes
25 activos tales como agentes reductores del colesterol. Como tal, estos compuestos pueden ser útiles en la fabricación de nutraceuticos y/o alimentos funcionales útiles para impedir las condiciones asociadas con la hiperlipidemia.

En una modalidad preferida, los compuestos de poliglucosamina y fibrato se incorporan en alimentos funcionales que incluyen pero no se limitan a, bebidas, incluyen pero sin limitarse a
5 sodas, agua, bebidas de energía/deportes, jugos enlatados o embotellados, jugos frescos y refrigerados, jugos congelados, bebidas de yogurt, bebidas suaves, té, y café; panes y granos, incluyendo pero sin limitarse a cereales de desayuno, panes, bienes horneados, ingredientes de productos horneados
10 tales como harina, panes congelados, panes secos y galletas, pastas; productos de snack, incluyendo pero sin limitarse a barras de nutrición, barras para pérdida de peso, barras para dar energía/deportes, barras de dulces, pastillitas, chicles; comidas empacadas y preparadas, incluyendo pero sin limitarse
15 a comidas congeladas tales como pizzas y cenas, sopas enlatadas y secas, postres incluyendo galletas; condimentos, incluyendo pero sin limitarse a aderezos, salsas; alternativas de envase de leche, incluyendo pero sin limitarse a, leche, queso, mantequilla, helado de crema,
20 yogurt, margarina y leche de soya.

Dosificaciones

Una dosis diaria total de fibrato puede en general estar en
25 el rango entre aproximadamente 50 mg/día hasta aproximadamente 1200 mg/día en dosis únicas o divididas. Ciertas modalidades con respecto a la dosificación apropiada, se muestran en la tabla 1.

Tabla 1

Frecuencia de administración	DOSIFICACIÓN POR ADMINISTRACIÓN						
	HEP	Ciprofibrato	Fenofibrato	Fenofibrato o (micro lipidilo)	Finofibrato o (supra lipidilo)	Gemfibrozil	Benza fibrato
Una vez por día (1 a 3 cápsulas)	600 a 2400 mg	50 a 100 mg	50 a 300 mg	70 a 300 mg	50 a 200 mg	600 a 1200 mg	200 a 400 mg
Por cápsula	200 a 800 mg	16 a 100 mg	16 a 300 mg	23 a 300 mg	16 a 200 mg	200 a 600 mg	66 a 400 mg
Dos veces por día (1 a 2 cápsulas)	400 a 1200 mg	25 a 50 mg	25 a 150 mg	35 a 150 mg	25 a 100 mg	300 a 600 mg	100 a 200 mg
Por cápsula	200 a 800 mg	12.5 a 50 mg	12.5 a 160 mg	18 a 150 mg	12.5 a 100 mg	150 a 600 mg	50 a 200 mg

5 En el caso de sales de fibrato farmacéuticamente aceptables, los pesos indicados anteriormente se refieren al peso del ácido equivalente o la base equivalente del compuesto terapéutico derivado de la sal.

10 Para una poliglucosamina, una dosis diaria total de aproximadamente 400 ,g hasta aproximadamente 4.8 gramos por día y preferiblemente entre aproximadamente 800 mg y aproximadamente 2.4 gramos por día puede en general ser lo apropiado. En una modalidad, la poliglucosamina se puede 15 administrar en aproximadamente 400 mg por día. La poliglucosamina se toma preferiblemente tres veces al día. La poliglucosamina preferiblemente se toma con los alimentos.

Ciertas dosificaciones

Como se utiliza aquí, el término "dosis diaria total" se refiere a la cantidad de composición administrada a un individuo en un día.

El término "dosis" se refiere a la cantidad de composición administrada a un individuo de una sola vez.

El término "dosis unitaria" se refiere a la cantidad de una composición pre-empacada por el fabricante o el de la farmacia en cantidades estandarizadas. Así, por ejemplo, la dosis de ingredientes en una tableta o cápsula única pudiera considerarse una única "dosis unitaria" mientras en una o más tabletas o cápsulas se toman simultáneamente.

En otra modalidad, una poliglucosamina se administra con una dosis diaria total de aproximadamente 600 mg hasta aproximadamente 2400 mg y un fibrato se administra en una dosis diaria total de aproximadamente 50 mg hasta aproximadamente 1200 mg. Preferiblemente, la dosis diaria total se administra una vez por día en aproximadamente 1 a 3 dosis unitarias, preferiblemente en forma de cápsula. De acuerdo con lo anterior, cada dosis unitaria puede contener alrededor de 200 mg hasta aproximadamente 1200 mg de poliglucosamina. También, cada dosis unitaria puede contener cerca de 16 mg hasta aproximadamente 600 mg de fibrato. En una modalidad la dosis diaria total se administra en dos

dosis unitarias administradas una vez por día; la dosis unitaria contiene aproximadamente 600 mg de poliglucosamina y por lo menos aproximadamente 50 mg de fibrato. La dosis se administra preferiblemente con las comidas.

5

En otra modalidad, la dosis diaria total se administra en dos dosis por día. En cada dosis, hay una poliglucosamina en una cantidad de aproximadamente 200 mg hasta aproximadamente 1200 mg y un fibrato en una cantidad de aproximadamente 50 mg hasta aproximadamente 40 mg. Preferiblemente, la dosis diaria total se administra en dos dosis por día con aproximadamente 1 a 2 dosis unitarias por dosis. De acuerdo con lo anterior, cada dosis unitaria puede contener aproximadamente 200 mg a aproximadamente 600 mg de poliglucosamina. También, cada dosis unitaria puede contener aproximadamente 25 mg a aproximadamente 600 mg de fibrato. En una modalidad, la dosis unitaria se administra en una cápsula administrada dos veces al día; la dosis unitaria contiene aproximadamente 600 mg por glucosamina y aproximadamente 50 mg de fibrato. La dosis se administra preferiblemente con las comidas.

El régimen de dosificación para tratar la hiperlipidemia y las condiciones asociadas a la hiperlipidemia, y reducir el colesterol en el plasma con la terapia de combinación y las composiciones farmacéuticas de las modalidades preferidas se selecciona de acuerdo con una variedad de factores. Estos factores incluyen, pero no se limitan a, el tipo, edad, peso, sexo, dieta, y afección médica del paciente, la severidad de

la enfermedad, la vía de administración, las consideraciones farmacológicas, tales como la actividad, eficacia, farmacocinéticas y perfiles de toxicología del compuesto particular empleado, sea que se utilice un sistema de suministro de droga, y sea que el compuesto se administre como parte de una combinación de drogas. Así, el régimen de dosificación realmente empleado puede variar ampliamente y por lo tanto desviarse del régimen de dosificación preferido establecido anteriormente.

10

El tratamiento inicial de un paciente que sufre de una afección hiperlipidémica, tal como, pero sin limitarse a, hipercolesterolemia, aterosclerosis, enfermedad coronaria del corazón, y enfermedades cardiovasculares, puede comenzar con las dosificaciones indicadas anteriormente. El tratamiento debería en general continuarse lo necesario durante un periodo de varias semanas a varios meses o años hasta que la afección se haya controlado o eliminado. Los pacientes bajo el tratamiento con los compuestos o composiciones descritos aquí se pueden monitorear rutinariamente mediante, por ejemplo, medir el LDL del suero y los niveles de colesterol total mediante cualquiera de los métodos bien conocidos en la técnica, para determinar la efectividad de la terapia de combinación.

25

Kits

Las modalidades preferidas también se relacionan con kits para dispensar convenientemente la terapia de combinación. Estos kits preferiblemente contienen una pluralidad de dosis diarias del fibrato y de la poliglucosamina. Las dosis diarias son formas de dosificación preferiblemente separadas de cada medicamento. Las instrucciones también se suministran para el paciente y/o para el médico o farmacólogo que atiende. Los kits pueden contener suministros para un tiempo de duración dado de tratamiento tal como un mes.

10

El empaque tipo ampollas con siete días de tratamiento, cada día indicado (lunes, martes, miércoles, jueves, viernes, sábado, domingo). Cada día tiene dos cápsulas o tabletas. Una indicada como "desayuno", la otra indicada como "cena".

15 Existe un total de 14 cápsulas por paquete de ampollas (dos filas y siete columnas) y cuatro ampollas en una caja, suficiente para un suministro de 4 semanas (28 días). Alternativamente, usted podría tener una única fila para una dosificación de una sola vez al día (solamente en la cena), o

20 tres filas para tres veces por días (desayuno, almuerzo, cena). De acuerdo con esta modalidad, el fibrato y la poliglucosamina están contenidas en la misma cápsula o tableta.

25 De acuerdo con otra modalidad, el fibrato y la poliglucosamina están en tabletas o cápsulas separadas, una dosis por día de cada una, para cada uno de los siete días.

Esto representaría dos filas y siete columnas por ampolla, con cuatro ampollas por caja.

Aquellos versados en la técnica pueden conocer, o ser capaces de determinar, utilizando no más que la experimentación de rutina, muchos equivalentes de las modalidades específicas de la invención descritas aquí. Estos y otros equivalentes tienen el propósito de estar abarcados por las siguientes reivindicaciones.

10

Aunque la presente invención se ha explicado anteriormente mediante una modalidad preferida de la misma, se debería estacar que cualquier modificación a esta modalidad preferida dentro del alcance de las reivindicaciones adjuntas no altera o cambia la naturaleza y alcance de la presente invención.

Ejemplo 1

1.0 RESUMEN DEL ENSAYO

20

Nombre del producto estudiado	HEP-40™ (40 kDa, 93% desacetilado, poliglucosamina)
Título del ensayo	Un placebo controlado doblemente oculto de doce semanas alegorizado en el estudio piloto que evalúa la efectividad del HEP-40™ co-administrado con un fibrato en pacientes con hipercolesterolemia persistente bajo una monoterapia de fibrato.
Inicio y duración estimada del ensayo	Tratamiento: 12 semanas
Hipótesis	Principal: En pacientes con hipercolesterolemia persistente definida de acuerdo con el objetivo LDL-C anterior mientras está en

	monoterapia con fibrato, un curso de 12 semanas de 800 mg bid de HEP-40™ co-administrado con el fibrato actual producirá una reducción significativamente mayor en LDL-C del suero circulante cuando se comparó con el placebo. Secundaria: i. En pacientes con hipercolesterolemia persistente definida de acuerdo con el objetivo LDL-C anterior mientras está en monoterapia con fibrato, un curso de 12 semanas de 800 mg bid de HEP-40™ co-administrado con el fibrato actual producirá una reducción significativamente mayor los siguientes parámetros del lípido cuando se comparó con el placebo: • Triglicéridos • Colesterol total • C-proteína reactiva En pacientes con hipercolesterolemia persistente definida de acuerdo con el objetivo LDL-C anterior mientras está en monoterapia con fibrato, un curso de 12 semanas de 800 mg bid de HEP-40™ co-administrado con el fibrato actual puede ser bien tolerado y seguro.
Objetivo principal	En pacientes con hipercolesterolemia persistente como se dijo anteriormente con objetivo recomendado de LDL-C mientras está en monoterapia con fibrato: Para comparar la efectividad de un curso de doce semanas de 800 mg bid de HEP-40™ contra el placebo co-administrado con el fibrato actual en la reducción del LDL-C circulante en el suero
Objetivo secundario	En pacientes con hipercolesterolemia persistente como se dijo anteriormente con objetivo recomendado de LDL-C mientras está en monoterapia con fibrato: i. Comparar la efectividad de 800 mg bid de HEP-40™ contra el placebo con-administrado con el fibrato actual en una dosis no alterada

	para reducir los siguientes parámetros de lípidos: • Triglicéridos • Colesterol total • C-proteína reactiva ii. para determinar la seguridad y tolerabilidad de un curso de 12 semanas de 800 mg bid de HEP-40TM co-administrado con el fibrato actual.
Fase clínica	Estudio piloto en fase IV
Diseño del ensayo	Un placebo controlado doblemente oculto de doce semanas aleatorizado. Pacientes con hiperlipidemia persistente definida como niveles de LDL- C por encima del objetivo recomendado mientras están en una monoterapia con fibrato serán enlistados. Los pacientes deben estar en terapia con fibrato durante más de cuatro semanas pero menos de 6 meses. Los pacientes serán aleatorizados en una proporción de 1:1 para ser tratados con: • HEP-40 en 800 mg bid co-administrados en su fibrato actual durante 12 semanas (HEP-40). • Placebo bid co-administrado con su fibrato actual durante 12 semanas (PLACEBO)
Número de pacientes que van a ser incluidos	Por lo menos 20 pacientes serán enlistados y aleatorizados. Por lo menos 14 pacientes evaluables son requeridos.
Formulación, vía de administración y dosificación	El tratamiento con fibrato se continuará según su entrada al estudio anterior. La droga bajo estudio (HEP-40 o el placebo) será administrada oralmente durante las comidas. El placebo y el HEP-40 pueden ser similares en formulación, apariencia y gusto
Duración del tratamiento	12 semanas de HEP-40 TM o placebo co-administrado con la dosis de fibrato actual.

REIVINDICACIONES

1. Una forma de dosificación farmacéutica que comprende en combinación:
- 5
- a) Una cantidad farmacéuticamente efectiva de fibrato;
- b) Una cantidad farmacéuticamente efectiva de poliglucosamina; y opcionalmente
- 10 c) Un portador farmacéuticamente aceptable.
2. La forma de dosificación de acuerdo con la reivindicación 1, en donde la poliglucosamina tiene un peso molecular que varía entre cerca de 30 kDa a
- 15 aproximadamente 50 kDa.
3. La forma de dosificación de acuerdo con la reivindicación 1 o 2, en donde la poliglucosamina tiene un grado de desacetilación que varía entre
- 20 aproximadamente 80% a aproximadamente 100%.
4. La forma de dosificación de acuerdo con la reivindicación 3, en donde la poliglucosamina tiene un peso molecular de aproximadamente 30 kDa y un
- 25 grado de desacetilación de aproximadamente 89%.

5. La forma de dosificación de acuerdo con la reivindicación 4, en donde la poliglucosamina es Libracol®.
- 5 6. La forma de dosificación de acuerdo con la reivindicación 3, en donde la poliglucosamina tiene un peso molecular de aproximadamente 40 kDa y un grado de desacetilación de por lo menos 80%.
- 10 7. La forma de dosificación de acuerdo con una cualquiera de las reivindicaciones 1 a 6, en donde el fibrato es fenofibrato.
- 15 8. La forma de dosificación de acuerdo con una cualquiera de las reivindicaciones 1 a 7, en donde esta comprende por lo menos aproximadamente 25 mg de fibrato por forma de dosis por día.
- 20 9. La forma de dosificación de acuerdo con una cualquiera de las reivindicaciones 1 a 8, en donde esta comprende por lo menos 400 mg de poliglucosamina por forma de dosificación por día.
- 25 10. La forma de dosificación de acuerdo con una cualquiera de las reivindicaciones 1 a 9, para impedir o tratar la hiperlipidemia y la afección asociada con hiperlipidemia.

11. La forma de dosificación de acuerdo con la reivindicación 10, en donde la afección asociada con hiperlipidemia se selecciona del grupo que consiste de hipercolesterolemia, aterosclerosis, enfermedad coronaria del corazón, y enfermedad cardiovascular.

12. Una composición farmacéutica útil en la prevención o tratamiento de la hiperlipidemia y la afección asociada con la hipercolesterolemia, la composición farmacéutica comprende por lo menos:

- Una cantidad farmacéuticamente efectiva de fibrato;
- Una cantidad farmacéuticamente efectiva de poliglucosamina; y
- Un portador farmacéuticamente aceptable.

13. La composición de acuerdo con la reivindicación 12, en donde la poliglucosamina tiene un peso molecular que varía de aproximadamente 30 kDa a aproximadamente 50 kDa.

14. La composición de acuerdo con la reivindicación 12 o 13, en donde la poliglucosamina tiene un grado de desacetilación que varía de aproximadamente 90% a aproximadamente 100%.

15. La composición de acuerdo con la reivindicación 14, en donde la poliglucosamina tiene un peso molecular

de aproximadamente 30 kDa y un grado de desacetilación de aproximadamente 89%.

5 16. La composición de acuerdo con la reivindicación 14, en donde la poliglucosamina tiene un peso molecular de aproximadamente 40 kDa y un grado de desacetilación de por lo menos 80%.

10 17. La composición de acuerdo con la reivindicación 15, en donde la poliglucosamina es Libracol®.

18. La composición de acuerdo con una cualquiera de las reivindicaciones 12 a 17, en donde el fibrato es fenofibrato.

15 19. La composición de acuerdo con una cualquiera de las reivindicaciones 12 a 18, en donde la cantidad farmacéuticamente efectiva de fibrato es de por lo menos aproximadamente 25 mg.

20 20. La composición de acuerdo con una cualquiera de las reivindicaciones 12 a 19, en donde la cantidad farmacéuticamente efectiva de poliglucosamina es por lo menos 400 mg.

25 21. La composición de acuerdo con una cualquiera de las reivindicaciones 12 a 20, la prevención o tratamiento

de la hiperlipidemia y la afección asociada con la hiperlipidemia.

22. La composición de acuerdo con la reivindicación 21,
5 en donde la afección asociada con la hiperlipidemia selecciona del grupo que consiste de hipercolesterolemia, aterosclerosis, enfermedad coronaria del corazón, y enfermedad cardiovascular.

10 23. Un método para prevenir o tratar la hiperlipidemia en un mamífero que comprende administrar a dicho mamífero una cantidad efectiva de una forma de dosificación según la reivindicación 1, o la composición de la reivindicación 12.

15

24. El método de acuerdo con la reivindicación 23, en donde la cantidad de fibrato administrada al mamífero es de por lo menos aproximadamente 50 mg por día.

20 25. El método de acuerdo con la reivindicación 23 o 24, en donde la cantidad de poliglucosamina administrada al mamífero es de por lo menos 600 mg por día.

25 26. El método de acuerdo con una cualquiera de las reivindicaciones 23 a 25, en donde el mamífero es un humano.

27. El método para reducir el colesterol en la sangre en una mamífero, en donde dicho método comprende la etapa de administrar a dicho mamífero una cantidad efectiva de la forma de dosificación de la reivindicación 1 o la composición de la reivindicación 12.

28. El método de acuerdo con la reivindicación 27, en donde la cantidad de fibrato administrada al mamífero es de por lo menos 50 mg por día.

29. El método de acuerdo con la reivindicación 27 o 28, en donde la cantidad de poliglucosamina administrada al mamífero es de por lo menos 600 mg por día.

30. El método de acuerdo con una cualquiera de las reivindicaciones 27 a 29, en donde el mamífero es un humano.

31. Un alimento funcional que comprende una cantidad efectiva de poliglucosamina y una cantidad efectiva de fibrato.

32. El alimento funcional de acuerdo con la reivindicación 31 seleccionado del grupo que consiste de bebidas, pan, granos, alimentos de pasabocas, alimentos preparados y empacados, condimentos, y leche y alternativas de la leche.

33. El alimento funcional de acuerdo con la reivindicación 31 o 32, en donde la poliglucosamina tiene un peso molecular que varía entre aproximadamente 30 kDa a aproximadamente 50 kDa.

34. El alimento funcional de acuerdo con una cualquiera de las reivindicaciones 31 a 33 en donde la poliglucosamina tiene un grado de desacetilación que varía entre cerca de 80% a 100%.

35. El alimento funcional de acuerdo con una cualquiera de las reivindicaciones 31 a 34, en donde la poliglucosamina tiene un peso molecular de aproximadamente 30 kDa y un grado de desacetilación de aproximadamente 89%.

36. El alimento funcional de acuerdo con la reivindicación 35, en donde la poliglucosamina es Libracol®.

37. La forma de dosificación de acuerdo con una cualquiera de las reivindicaciones 31 a 36 en donde el fibrato es fenofibrato.

38. El alimento funcional de acuerdo con una de las reivindicaciones 31 o 37, en donde este comprende por lo menos aproximadamente 25 mg de fibrato.

39. El alimento funcional de acuerdo con la reivindicación 38, en donde este comprende por lo menos 400 mg de poliglucosamina.

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40. Un kit para la profilaxis o tratamiento de la hiperlipidemia en un mamífero, el kit comprende una pluralidad de dosis diarias de las formas de dosificación de un fibrato y una poliglucosamina junto con instrucciones para un régimen de tratamiento.

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41. El kit de acuerdo con la reivindicación 40, en donde la dosis diaria de fibrato es de por lo menos 50 mg por día.

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42. El kit de acuerdo con la reivindicación 41, en donde la dosis diaria de poliglucosamina es de por lo menos 600 mg por día.

COMBINACIÓN DE POLIGLUCOSAMINA Y FIBRATO PARA LA PREVENCIÓN Y
TRATAMIENTO DE LA HIPERLIPIDEMIA

Resumen

5

La presente invención se relaciona con composiciones
farmacéuticas que comprenden un fibrato (por ejemplo
ciprofibrato, gemfibrozil, benza fibrato, y fenofibrato) y una
poliglucosamina (por ejemplo chitosan) que tiene pesos
10 moleculares menores a 650 kDa y grados de desacetilación de
entre 70% a 100%. También se describen los usos de dichas
composiciones para el tratamiento de la hiperlipidemia y
afecciones asociadas (por ejemplo hipercolesterolemia,
aterosclerosis, enfermedad coronaria del corazón y enfermedad
15 cardiovascular) o como alimentos funcionales.

PATENT COOPERATION TREATY

from the INTERNATIONAL SEARCHING AUTHORITY

To: ROBIC Centre CDP Capital 1001 Square Victoria Bloc E - Sieme Etage MONTREAL, Quebec Canada, H2Z 2B7		PCT NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION (PCT Rule 44.1)	
Applicant's or agent's file reference 012360-0014		Date of mailing (day/month/year) 18 January 2007 (18-01-2007) FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/CA2006/001603		International filing date (day/month/year) 28 September 2006 (28-09-2006)	
Applicant DNP CANADA INC. ET AL			
1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith. Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46): When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report. Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70 For more detailed instructions, see the notes on the accompanying sheet. 2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith. 3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that: ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices. ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made. 4. Reminders Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for the international publication. The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date. Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the <i>PCT Applicant's Guide</i>, Volume II, National Chapters and the WIPO Internet site.			
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476		Authorized officer Diane Leclaire 819-997-7623	

Form PCT/ISA/220 (October 2005)

(See notes on accompanying sheet)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)) :

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter :

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers;
claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended
claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: ROBIC Centre CDP Capital 1001 Square Victoria Bloc E - 8ieme Etage MONTREAL, Quebec Canada, H2Z 2B7		PCT WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)																	
Date of mailing 18 January 2007 (18-01-2007) <i>(day/month/year)</i>		FOR FURTHER ACTION See paragraph 2 below																	
Applicant's or agent's file reference 012360-0014																			
International application No. PCT/CA2006/001603	International filing date (day/month/year) 28 September 2006 (28-09-2006)	Priority date (day/month/year) 28 September 2005 (28-09-2005)																	
International Patent Classification (IPC) or both national classification and IPC IPC: <i>A61K 31/7008</i> (2006.01), <i>A61K 31/216</i> (2006.01), <i>A23L 1/30</i> (2006.01), <i>A61K 31/722</i> (2006.01), <i>A61P 3/06</i> (2006.01).																			
Applicant DNP CANADA INC. ET AL																			
1. This opinion contains indications relating to the following items : <table border="0"> <tr> <td>☒ Box No. I</td> <td>Basis of the opinion</td> </tr> <tr> <td>☐ Box No. II</td> <td>Priority</td> </tr> <tr> <td>☒ Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td>☐ Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td>☒ Box No. V</td> <td>Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td>☐ Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td>☐ Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td>☒ Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> 2. FURTHER ACTION If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered. If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. For further options, see Form PCT/ISA/220. 3. For further details, see notes to Form PCT/ISA/220.				☒ Box No. I	Basis of the opinion	☐ Box No. II	Priority	☒ Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	☐ Box No. IV	Lack of unity of invention	☒ Box No. V	Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	☐ Box No. VI	Certain documents cited	☐ Box No. VII	Certain defects in the international application	☒ Box No. VIII	Certain observations on the international application
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☐ Box No. VI	Certain documents cited																		
☐ Box No. VII	Certain defects in the international application																		
☒ Box No. VIII	Certain observations on the international application																		
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Carleton Place, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476		Date of completion of this opinion 18 December 2006 (18-12-2006)																	
		Authorized officer C. Bourque 819-934-3596																	

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2006/001603

No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search.
- 3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments :

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2006/001603

No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application
☒ claim Nos. 23 - 30

because:

- ☒ the said international application, or the said claim Nos. 23 - 30 relate to the following subject matter which does not require an international search (*specify*):

The subject matter of claims 23 - 30 relate to methods of medical treatment of the human or animal body (Rule 39.1(iv) of the PCT). For the assessment of these claims with respect to their industrial applicability (Article 33(4) of the PCT), no unified criteria exists in the PCT. The patentability of the subject matter defined by these claims in the different member states may depend on the formulation of the claims. Certain national offices accept claims worded as methods of medical treatment, while other offices accept claims worded as use claims. Accordingly, this written opinion has been established with regard to the alleged effects or purposes/uses of the compounds defined in claims 23 - 30.

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claim Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

- ☐ no international search report has been established for said claims Nos.

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- ☐ See Supplemental Box for further details.

No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statements:

Novelty (N)	Claims 2, 5 - 8, & 10 - 39	YES
	Claims 1, 3, 4, 9, & 40 - 42	NO
Inventive step (IS)	Claims 2, 5, 6, 13, 15 - 17, & 31 - 39	YES
	Claims 1, 3, 4, & 7 - 12, 14, 18 - 30, & 40 - 42	NO
Industrial applicability (IA)	Claims None	YES
	Claims 1 - 42	NO

2. Citations and explanations:

Citations:

- D1 (Martinac *et al.*, Eur. J. Pharm. Sci., Vol 17, pp. 207-216, 2002) discloses pharmaceutical formulations comprising gemfibrozil, low molecular weight chitosans (150 - 600 kDa) having various degrees of deacetylation (e.g. 83, 83.5, 84, 87.4, and 91 %), with pharmaceutically acceptable polymers (PHPA or HPMC). D1 further discloses that gemfibrozil is a lipid-regulating agent (D1: p 207, para 1), and that "chitosan itself reduces blood cholesterol levels and thus it could be expected that entrapment of gemfibrozil into chitosan microspheres could potentiate that effect" (D1: p 208, left col., lines 25 - 28).
- D2 (Remuñán-López *et al.*, Proceed. Intern. Symp. Control. Rel. Bioact. Mater., Vol 22, pp. 430-431, 1995) discloses chitosan encapsulated drugs such as clofibrate.
- D3 (Jorgensen *et al.*, WO 98/22114) discloses combinations of chitosan and fibrates (See D3: pp. 37 and 76).
- D4 (Merck Index, 11th Ed. entry 3924, pp. 624-625) discloses fenofibrate and the efficacy thereof in hyperlipidemias.

Novelty:

Claims 1, 3, 4, 9, and 40 - 42 do not comply with Article 33(2) of the PCT. Each of D1, D2, and D3 disclose compositions comprising fibrates and chitosan. D1 further discloses chitosans compositions having various degrees of deacetylation (e.g. 83, 83.5, 84, 87.4, and 91 %) and pharmaceutically acceptable polymers. Claims 1, 3, 4, 9, and 40 - 42 thus broadly define compositions that encompass the prior art.

Claims 2, 5 - 8, 10 - 39 comply with Article 33(2) of the PCT. No single prior art document discloses compositions comprising fibrates and polychitosamines having molecular weights of 30 to 50 kDa or the utility of said compositions in the treatment of hyperlipidemia or as functional foods.

(Continued in Supplemental Box ...)

No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

In the Description:

The description does not comply with Article 5 of the PCT. The http address (<http://www.wnbc.com/dnmaxgomez/393553/details>) provided on page 4, line 9, is no longer active, and no archived pages have been stored on internet archive sites, such as <http://www.archive.org/web/web.php>. The information disclosed in the cited http file is thus no longer available to the public.

The description does not comply with Article 5 of the PCT. The statement found on page 12, line 31, which incorporates by reference another document, does not comply with Article 5 of the PCT. The description should be complete in and of itself. A person skilled in the art should be able to understand the patent specification without reference to any other document.

The description does not comply with Article 5 of the PCT. The documents referred to on page 15, line 25 - 26; page 15, line 30; and page 16, lines 1 - 2; are not fully identified and therefore are not accessible by the public. The applicant must fully identify the documents referred to in the description. Non-patent documents so referred to should be identified by title, author, date, and source.

The description does not comply with Article 5 of the PCT. The description does not provide sufficient information and guidance to enable a person skilled in the art to successfully practice the alleged invention over its entire scope with expectation of success. The applicant has submitted a summary of a proposed formulations (e.g. pharmaceutical dosage forms or functional foods) and a clinical trial without supplying the results of said clinical trial or any specific examples of formulations prepared by the applicant. Without clear support for the credible utility of the claimed subject matter, the support in the description is regarded as speculative.

The statements found on page 23, lines 12 - 21, of the description does not comply with Article 6 of the PCT. These are general statements which imply that the extent of protection may be expanded in some vague and imprecise way.

The description does not comply with Rule 11.2(a) of the PCT. The scheme on page 13 (lines 15 - 22) is illegible.

The description does not comply with Rule 11.9(d). The point size of the text in Table 1 (page 21) is too small. Furthermore, the examiner notes that on pages 6, 8, 9, 11, 18, 19, 20, 22, and 23 of the description, the last line of text has been compressed in the document on file, thus causing a lack of clarity when reading said text.

In the Claims:

Claims 1 and 31 do not comply with Article 6 of the PCT. The use of the expressions "pharmaceutically effective amount" and "effective amount" are ambiguous as said claims do not encompass any particular pharmaceutical or functional use.

Claims 4, 6, 15, 16, 34 and 35 are unclear and do not comply with Article 6 of the PCT. The double inclusion of any element renders the claims indefinite. The expression "degree of decacetylation" in said claims was defined previously in claims 3, 14, and 34. Similarly, the expression "molecular weight" in claims 4, 6, 15, 16, 34 and 35 was defined previously in claims 2, 13, and 33. The aforementioned expressions should therefore be referred to using a definite article in the dependent claims.

Claims 5, 17, and 36 do not comply with Article 6 of the PCT. Trademarks and similar expressions characterize the commercial origin of goods rather than the compositions and/or properties of said goods, which may change over time. Reference to the trademark Libracol™ should be amended to the actual compound/ composition to which the present trademark refers.

Claims 8, 9, 38, and 39 do not comply with Article 6 of the PCT. The inclusion of the indefinite article "a" causes ambiguity in the claims.

Claims 8, 19, 24, and 38 are indefinite and does not comply with Article 6 of the PCT. The inclusion of "at least about" causes ambiguity.

(Continued in Supplemental Box ...)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box V & Box VIII**

Continuation of Box V:

Inventive Step:

Claims 1, 3, 4, 9, and 40 - 42 do not comply with Article 33(3) of the PCT. As D1, D2, and D3 are novelty destroying for the subject matter of these claims, said claims also lack an inventive step.

Claims 7, 8, 10 - 12, 14, and 18 - 30, not comply with Article 33(3) of the PCT. The prior art document D1 discloses compositions comprising a fibrate and polychitosamine. D1 also infers the utility of the fibrate-polychitosamine combination in the regulation of blood cholesterol and lipid levels (See D1: p. 207, para. 1; and p. 208, left col., lines 25 - 28). Thus, it requires no inventive ingenuity on the part of the person skilled in the art to apply the compositions of D1 in the regulation of blood cholesterol and lipid levels as claimed by the applicant. Claims, 8, 10 - 12, 14, and 19 - 30, thus lack an inventive step. Furthermore, the substitution of one fibrate for another (i.e. the gemfibrozil of D1 for the fenofibrate of D4) lacks inventive ingenuity as the present disclosure does not identify any unexpected and surprising result that arises from the selection of fenofibrate (D4) over the gemfibrozil of D1. Claims 7 and 18 thus also lack an inventive step.

Claims 2, 5, 6, 13, 15 - 17, and 31 - 39 appear to comply with Article 33(3) of the PCT as the prior art does not suggest compositions comprising fibrates and polychitosamines having molecular weights of 30 to 50 kDa, and the utility of said compositions in the treatment of hyperlipidemia or as functional foods.

Industrial applicability:

The present application fails to provide any credible and factual support on which this international search authority can arrive at a finding of practical utility for the alleged invention. The present application discloses the alleged invention in speculative terms, and in terms of the predicted results of a proposed clinical trial and envisioned formulations of pharmaceutical dosage forms and functional foods. Exemplary pharmaceutical dosage forms and functional foods are not provided nor any clinical results from said clinical trial. Thus the applicant has not demonstrated any evidence that the claimed combinations were prepared and did work as predicted. Without said evidence, the claimed subject matter of claims 1 - 42 does not comply with article 33(4) of the PCT.

Continuation of Box VIII:

Claims 12 - 22 lack conciseness and do not comply with Article 6 of the PCT for failing to state additional features. The claims should differ from one another. The claims 10 and 11, as they read on claims 1 - 9, are identical or are so close in content to claims 12 - 22 that these claims address the same subject matter.

Claim 37 is unclear and does not comply with Article 6 of the PCT. The expression "dosage form" lacks a proper antecedent basis in any of claims 31 - 36.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 012360-0014

Box No. I TITLE OF INVENTION
COMBINATION OF POLYCHITOSAMINE AND FIBRATE FOR THE PREVENTION AND TREATMENT OF
HYPERLIPIDEMIA

Box No. II APPLICANT ☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DNP CANADA INC.
2000 MANSFIELD, SUITE 700
MONTRÉAL, QC
CANADA, H3A 2Z4

Telephone No.
(514) 276-3199

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

CA

State (that is, country) of residence:

CA

This person is applicant
for the purposes of:

☐ all designated
States

☒ all designated States except
the United States of America

☐ the United States
of America only

☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

AUBE, André
42, 1ÈRE RUE MONT-SUISSE
ST-SAUVEUR, QC
CANADA, J0R 1R2

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (if this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

CA

State (that is, country) of residence:

CA

This person is applicant
for the purposes of:

☐ all designated
States

☐ all designated States except
the United States of America

☒ the United States
of America only

☐ the States indicated in
the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ROBIC
CENTRE CDP CAPITAL
1001, SQUARE VICTORIA
BLOC E - 8e ÉTAGE
MONTRÉAL, QC
CANADA, H2Z 2B7

Telephone No.
(514) 987-8242

Facsimile No.
(514) 845-7874

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BRZEZINSKI, Ryszard 2200 DESCARTES SHERBROOKE, QC CANADA, J1J 4A8	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: CA	State (that is, country) of residence: CA
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) DUPUIS, Gilles 1424 BÉTHUNE STREET SHERBROOKE, QC CANADA, J1J 2A2	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: CA	State (that is, country) of residence: CA
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) LEHOUX, Jean-Guy 1220 DE L'ONTARIO STREET SHERBROOKE, QC CANADA, J1J 3S3	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: CA	State (that is, country) of residence: CA
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: 	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. However,

- ☐ DE Germany is not designated for any kind of national protection
☐ JP Japan is not designated for any kind of national protection
☐ KR Republic of Korea is not designated for any kind of national protection
☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application. See the Notes to Box No. V as to the consequences of such national law provisions in these States).

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 28/09/2005	60/721,102	US		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)).

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / CA

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of declarations

- ☐ Box No. VIII (i) Declaration as to the identity of the inventor :
☐ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :
☐ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :
☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America) :
☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):		Number of items
(a) on paper, the following number of sheets:		1. ☒ fee calculation sheet		1
request (including declaration sheets)	4	2. ☐ original separate power of attorney		
description (excluding sequence listing and/or tables related thereto)	27	3. ☐ original general power of attorney		
claims	5	4. ☐ copy of general power of attorney; reference number, if any:		
abstract		5. ☐ statement explaining lack of signature		
drawings		6. ☐ priority document(s) identified in Box No. VI as item(s):		
Sub-total number of sheets	36	7. ☐ translation of international application into (language):		
sequence listing		8. ☐ separate indications concerning deposited microorganism or other biological material		
tables related thereto		9. ☐ sequence listing in electronic form (Indicate type and number of carriers)		
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application):		
Total number of sheets	36	(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter		
		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column		
(b) ☐ only in electronic form (Section 801(a)(i))		10. ☐ tables in electronic form related to sequence listing (Indicate type and number of carriers)		
(i) ☐ sequence listing		(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application)		
(ii) ☐ tables related thereto		(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater)		
(c) ☐ also in electronic form (Section 801(a)(ii))		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column		
(i) ☐ sequence listing		11. ☐ other (specify):		
(ii) ☐ tables related thereto				
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the				
☐ sequence listing:				
☐ tables related thereto:				
(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)				

Figure of the drawings which should accompany the abstract: 0

Language of filing of the international application:

English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



ROBIC, PATENT AGENTS

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 17(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the international Bureau:

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

To:

ROBIC
Centre GDP Capital
1001, Square Victoria
Bloc E - 8e Etage
Montréal, Québec H2Z 2B7
CANADA

Date of mailing (day/month/year) 06 November 2006 (06.11.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 012360-0014	International application No. PCT/CA2006/001603

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

DNP CANADA INC. (for all designated States except US)
AUBE, André et al (for US)

International filing date: 28 September 2006 (28.09.2006)

Priority date(s) claimed: 28 September 2005 (28.09.2005)

Date of receipt of the record copy by the International Bureau: 26 October 2006 (26.10.2006)

List of designated Offices:

AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW

EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

ATTENTION: The applicant should carefully check the data appearing in this notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau. In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase - see updated important information (as of April 2002)
- requirements regarding priority documents (if applicable)

A copy of this notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Genève 20, Switzerland	Authorized officer Chahine Leila Facsimile No. +41 22 338 89 95 Telephone No. +41 22 338 88 91
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Facsimile No. +41 22 338 82 70

Form PCT/IB/301 (October 2005)

1/CIK/MYPE60

INFORMATION ON ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette* ("Section IV" part published on a weekly basis), to the *PCT Newsletter* (on a monthly basis) and to the relevant National Chapters in Volume II of the *PCT Applicant's Guide* (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages of the site, including those of the *Gazette*, *Newsletter* and *Guide*, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before the date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau and if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(xi)(b)).

PATENT COOPERATION TREATY

WO 2007/036044
PCT/CA2006/001603

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

ROBIC
Centre CDP Capital
1001, Square Victoria
Bloc E - 8e Etage
Montréal, Québec H2Z 2B7
CANADA

Date of mailing (day/month/year)

03 May 2007 (03.05.2007)

Applicant's or agent's file reference

012360-0014

IMPORTANT NOTICE

International application No.

PCT/CA2006/001603

International filing date (day/month/year)

28 September 2006 (28.09.2006)

Priority date (day/month/year)

28 September 2005 (28.09.2005)

Applicant

DNP CANADA INC. et al

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does apply, please see Form PCT/IB/308 (Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
05 April 2007 (05.04.2007)

CH

In accordance with Rule 47.1(c)-(bis)(ii), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

LU, SE, TZ, UG

In accordance with Rule 47.1(c)-(bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **20 MONTHS** from the priority date.

In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limits), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Athina Nickitas-Etienne

Facsimile No. +41 22 336 82 70

e-mail: pt04.pc1@wipo.int

Form PCT/IB/308 (First Notice) (January 2004)

PATENT COOPERATION TREATY

F the RECEIVING OFFICE

To: ROBIC Centre CDP Capital 1001 Square Victoria Bloc E - 8ieme Etage MONTREAL, Quebec Canada, H2Z 2B7		PCT NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE (PCT Rule 20.5(c))	
Applicant's or agent's file reference 012360-0014		IMPORTANT NOTIFICATION	
International application No. PCT/CA2006/001603	International filing date (day/month/year) 28 September 2006 (28-09-2006)	Priority date (day/month/year) 28 September 2005 (28-09-2005)	
Applicant DNP CANADA INC. ET AL			
Title of the invention COMBINATION OF POLYCHITOSAMINE AND FIBRATE FOR THE PREVENTION AND TREATMENT OF HYPERLIPIDEMIA			
1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above. 2. The applicant is further notified that the record copy of the international application: ☒ was transmitted to the International Bureau on <u>17 October 2006 (17-10-2006)</u> ☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*: ☐ because the necessary national security clearance has not yet been obtained. ☐ because (reason to be specified): * The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).			
Name and mailing address of the Receiving Office/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476		Authorized Officer Chantal Hébert (819) 953-4957	

Form PCT/RO/105 (July 1992; reprint January 2004)

PATENT COOPERATION TREATY

From **the RECEIVING OFFICE**

To:

ACT 18/13

The International Bureau of WIPO
34, chemin des Colombettes
1211, Geneva 20
Switzerland

PCT

NOTIFICATION OF DATE OF RECEIPT OF PRIORITY DOCUMENT OR OF PRIORITY APPLICATION NUMBER

(PCT Administrative Instructions,
Section 323(a), (b) and (c))

Applicant's or agent's file reference
012360-0014

Date of mailing 21 February 2007 (21-02-2007)
(day/month/year)

International application No.
PCT/CA2006/001603

International filing date 28 September 2006 (28-09-2006)
(day/month/year)

Applicant
DNP CANADA INC. ET AL

1. ☒ This receiving Office hereby gives notice of the receipt of the priority document(s) identified below on:

09 February 2007 (09-02-2007)

2. ☐ This receiving Office hereby gives notice of the receipt of a request (made under Rule 17.1(b)) to prepare and transmit to the International Bureau the priority document(s) identified below on:

Identification of the priority document(s):

Priority date

Priority application No.

Country or regional Office
or PCT receiving Office

28 September 2005
(28-09-2005)

60/721,102

US

Name and mailing address of the Receiving
Office/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street

Authorized Officer

Diane Leclaire 819-997-7623

Form PCT/RO/135 (July 1998; reprint January 2004)

108

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-032989-00000-0000

Fecha: 2008-04-02 16:28:46 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYI Eve: 378 FASENACIONAL
Act. 411 PRESENTACION Folios: 107

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION ☒ MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☒
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☒ INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐ INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐ INCOMPLETA ☐

FDO B

Firma Responsable

Fecha 02-02-08

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

P1127 109

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020.

Doctor(a)
RODRIGUEZ D^a ALEMÁN DILIA MARIA

REFERENCIA	Radicación No.	8 32909
	Solicitud internacional	PCT/CA2006/001603
	Fecha inicio fase nacional	28/04/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	- 5951

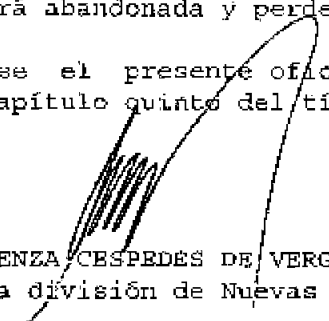
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENZA CESPÉDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 MAYO 2008
adpall